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(54) Phenylquinolinecarboxylic acids and derivatives as antitumor agents.

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Rad Jugosl. akad. znan. i umjet., kem., vol. 2, pages 93-101 (1983), Zagreb, YU; Yugoslav Symposium on Organic Chemistry, Febr. 17-19, 1981

Chemical and Pharmaceutical Bulletin, vol. 23, no. 1, 1975, pages 62-71, Tokyo, JP

CHEMICAL ABSTRACTS, vol. 67, 1967, page 10084, ref.nr. 107141g; Columbus, Ohio, US; K. KARZEL: "Effect of antiinflammatory agents on growth and multiplication of normal and neoplastic cells in vitro"

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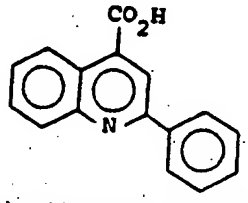
Description

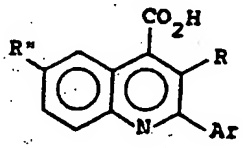
This invention relates to tumor inhibiting pharmaceutical compositions, there use for the manufacture of a medicament for inhibiting the growth of mammalian tumors, and phenylquinolinecarboxylic acids and derivatives thereof useful in such compositions and methods.

Cinchophen, 2-phenyl-4-quinoline carboxylic acid, has been known for many years and has been described as being useful as an antirheumatic and in the treatment of gout. Cinchophen has the formula:



Many cinchophen and cinchoninic acid derivatives have been prepared in investigating the Pfitzinger reaction and for use in color photographic developing.

Buu-Hoi *et al.* [*J. Chem. Soc.*, 386—8 (1953)] report 2-arylcinchoninic acids, prepared by the Pfitzinger reaction, having the formula:



where

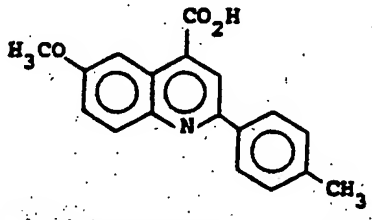
R = H, CH_3, C_2H_5 and phenyl;

Ar = fluoro-substituted phenyl; and

R'' = H, Br, Cl or CH_3.

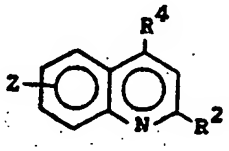
No use for these compounds is described.

Epling *et al.* [*Tet. Lett.*, *23* (38), 3843—3846 (1982)] report



as an intermediate to a new arylmethylsulfonyl chloride convertible to sulfonamides which can be photochemically cleaved.

Starke *et al.* in U.S. Patent 4,009,020, issued February 22, 1977, describe plant growth regulant cinchoninic acid derivatives, including those of the formula:



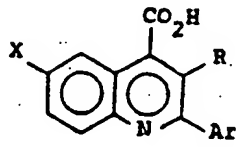
where

Z is H or halogen, preferably H;

R^2 is, *inter alia*, phenyl and halo-substituted phenyl; and

R^4 is CN, CO_2H and related esters and amides.

Buu-Hoi *et al. [J. Org. Chem., 18,* 1209—1224 (1953)] describe 2-arylcinchoninic acids of the formula:



where

X = H or Br;

R = H, CH_3, C_2H_5 and other groups; and

Ar can be a variety of aromatic groups including 4-biphenylyl, 4-alkylphenyl and 4-phenoxyphenyl.

The compounds prepared were part of a program to investigate the toxicity of cinchoninic acids and quinolines, since cinchophen ("Atophan") can produce a degeneration of liver tissue of a possible precancerous nature. Some of the compounds prepared caused degenerative changes in the liver.

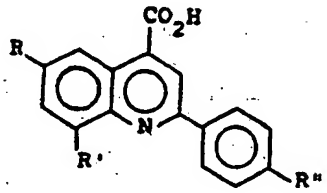
Buu-Hoi *et al. [Rec. trav. Chim., 62* 713—718 (1943)] report 2-(4-cyclohexylphenyl)cinchoninic acid and 2-(4-biphenylyl)cinchoninic acid. Hai *et al. [J. Org. Chem., 23,* 39—42 (1958)] describe 2-(4-cyclopentylphenyl)cinchoninic acids, including 3-methyl and 3-ethyl derivatives, and 6-bromo and 6-methyl derivatives. Buu-Hoi *et al. [J. Org., Chem., 22,* 668—671 (1957)] report 2-[4-(4-methoxy-3-chlorophenyl)phenyl]cinchoninic acid and its 3-methyl and 3-ethyl derivatives. Another Buu-Hoi report [*idem., 24,* 39—41 (1959)] describes the 2-methoxy-3-chlorphenyl isomer.

Yen *et al. [J. Org. Chem., 23* 1858—1861 (1958)] report 2-phenyl- and 2-(4-fluorophenyl)-6-fluorocinchoninic acids for testing as potential carcinogens.

Steinkopf *et al. [Annalen, 540,* 7—14 (1939); *idem, 543,* 119—128 (1940)] report 2-(5-methyl- and 5-phenyl-2-thienyl)cinchoninic acids. Sy *et al. [J. Chem. Soc.,* 1975—1978 (1954)] report 2-(5-*t*-butyl-2-thienyl)cinchoninic acid and its 3-methyl and 6-bromo derivatives.

Buu-Hoi *et al. [Rec. trav. Chim., 72,* 774—780 (1953)] report 2-[4-(4-hydroxy- and 4-methoxyphenyl)phenyl]cinchoninic acids and their 3-methyl derivatives.

Boykin *et al. [J. Med. Chem., 11,* 273—277 (1968)] report cinchoninic acids of the formula:



where

R = H, F, CH_3 or OCH_3;

R' = H, CH_3 or CF_3; and

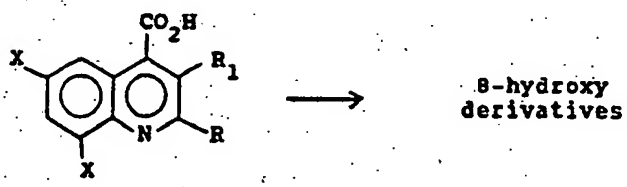
R'' = H, F, Cl, or CH_3 or OCH_3.

Although prepared as part of an antimalarial program, it does not appear that these intermediates were tested for antimalarial activity.

Saggiomo *et al. [J. Org. Chem., 11,* 277—281 (1968)] report antimalarial quinoline-4-methanols derived from the corresponding acids. The latter include 6,8-dichloro-2-(3-trifluoromethylphenyl)cinchoninic acid and ethyl ester, and 2-(4-chlorophenyl)-6-fluorocinchoninic acid and ethyl ester.

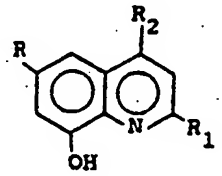
Buu-Hoi *et al. [Rec. trav. Chim., 70,* 825—832 (1951)] report 2-(4-*n*-propyl-4'-biphenylyl)cinchoninic acid and 3-methyl-2-(4-ethyl-4'-biphenylyl)cinchoninic acid.

Coles, in U.S. Patent 2,579,420, issued December 18, 1951, describes the conversion of 6,8-dihalocinchoninic acids into 6-halo-8-hydroxycinchoninic acids useful as color formers. Disclosed are compounds of the formula:



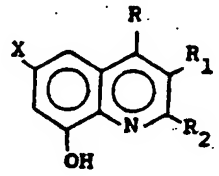
where
X is Cl or Br;
R_1 is, *inter alia*, H or lower alkyl; and
R is, *inter alia*, aryl and heteroaryl, optionally substituted by alkyl, aryl and the like.

Tulagin *et al.*, in U.S. Patent 2,524,741, issued October 3, 1950, describe the use, in color photographic developing, of 8-hydroxyquinolines of the formula:



where
R is halogen, NO_2 or SO_3H;
R_1 can be phenyl or phenyl substituted with Cl, CH_3, OCH_3 or NH_2; and
R_2 can be CO_2H.

French Patent 1,040,440 describes compounds similar to Tulagin *et al.*, useful in color photographic chemistry, of the formula:

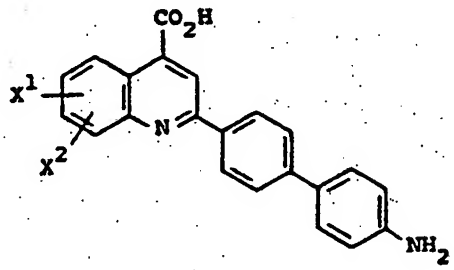


where
X is halogen;
R is CO_2H, $CONH_2$ or CONH-alkyl;
R_1 may be H or lower alkyl; and
R_2 may be aryl or a heterocyclic group.

German Patents 659,496; 668,741; and 668,742 describe 2-phenylcinchoninic acids, containing iodo groups and a free or etherified *p*-hydroxy substituent on the 2-phenyl group. Such compounds are stated to be useful as X-ray contrast agents.

Sakai *et al.*, *[Gann, 46,* 605—616 (1955)] report that 2-phenyl-4-carboxyquinoline has no tumoricidal effect in *in vitro* tests using NF mouse sarcoma.

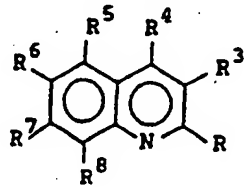
United States Patent 2,888,346 issued on May 26, 1959 to Tulagin and Hoffstadt describes compounds of the formula:



where
X^1 is 6-Cl or X^1 is 6-Cl and X^2 is 8-Br, and their use to protect organic media from damage from ultraviolet radiation.

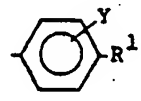
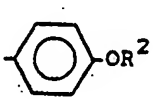
SUMMARY OF THE INVENTION

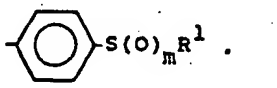
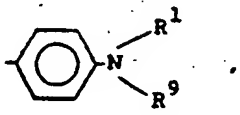
According to the present invention there is provided an antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound having the formula:

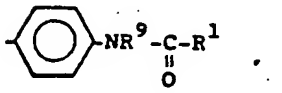
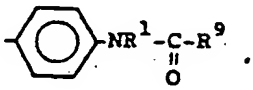


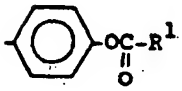
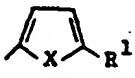
(I)

wherein

R is  .  .

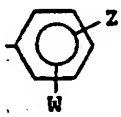
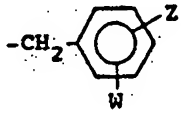
 .  .

 .  .

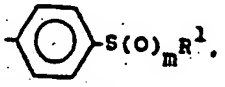
 . or  :

X is O, $S(O)_q$, NH or CH=N;

R^1 is $CH_3CH_2(CH_3)CH$, alkyl of 5—12 carbon atoms, alkenyl of 5—12 carbon atoms, cycloalkyl of 3—7 carbon atoms, cycloalkylalkyl of 5—12 carbon atoms, cycloalkenyl of 5—7 carbon atoms.

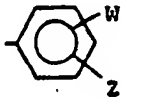
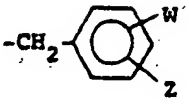
 or 

when R is



R^1 can be in addition alkyl of 3—4 carbon atoms;

R^2 is

 or  :

R^3 is H, alkoxy of 1—3 carbon atoms, alkylthio of 1—3 carbon atoms or alkyl of 1—3 carbon atoms optionally substituted with one or more of F, Cl, Br or $(CH_2)_pCOR^{10}$ where p is 1, 2, 3 or 4;

R^4 is CO_2H or CO_2R^{11};

R^5, R^6, R^7 and R^8 are independently H, F, Cl, Br, I, CH_3, CF_3, $S(O)_nR^{12}$ or CH_2CH_3, at least two of R^5, R^6, R^7, and R^8 being H;

R^9 and R^{9A} are independently H or alkyl of 1 to 3 carbon atoms;

R^{10} is OH, OCH_3, OCH_2CH_3, NH_2, $NHCH_3$ or $N(CH_3)_2$;

R^{11} is $(CH_2)_{2-4}NR^9R^{9A}$;

R^{12} is alkyl of 1—5 carbon atoms optionally substituted with one or more of F, Cl and Br;

W, Y and Z are independently H, F, Cl, Br, alkyl of 1—5 carbon atoms, NO_2, alkoxy of 1—5 carbon atoms, alkylthio of 1—5 carbon atoms, OH, CF_3 or NH_2;

m is 0 or 1;

n is 0 or 1; and

q is 0, 1 or 2;

or a pharmaceutically suitable salt thereof; with the following provisos:

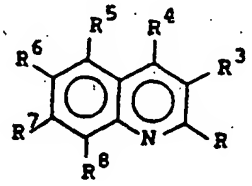
1) R^5, R^6 and R^7 cannot all be H;

2) when R^4 is $CO_2CH_2CH_2N(CH_3)_2$, R^5 is CH_2CH_3, or R^7 is Cl, R^1 cannot be cyclohexyl; and

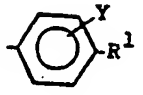
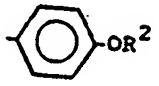
3) when R^1 is cyclohexyl and R^3 is H, R^6 must be Cl or F, but R^6 and R^8 cannot both be Cl.

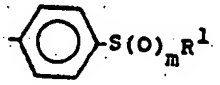
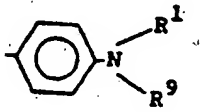
Also provided is their use for the manufacture of medicament for inhibiting the growth of mammalian tumors.

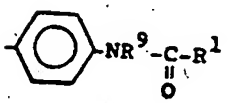
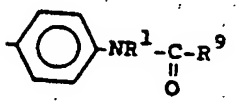
Additionally provided are novel antitumor active phenylquinoline carboxylic acids and derivatives having the formula:

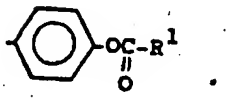
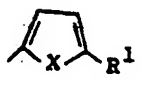


wherein

R is  .  .

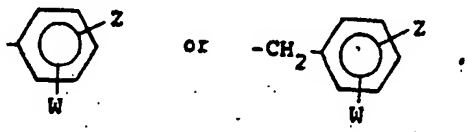
 .  .

 .  .

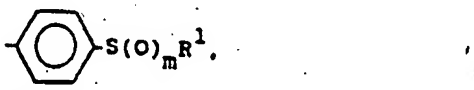
 . or  :

X is O, $S(O)_q$, NH or CH=N;

R^1 is $CH_3CH_2(CH_3)CH$, alkyl of 5—12 carbon atoms, alkenyl of 5—12 carbon atoms, cycloalkyl of 3—7 carbon atoms, cycloalkylalkyl of 5—12 carbon atoms, cycloalkenyl of 5—7 carbon atoms,

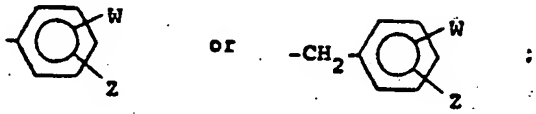


when R is



R^1 can be in addition alkyl of 3—4 carbon atoms;

R^2 is



R^3 is H, alkoxy of 1—3 carbon atoms, alkylthio of 1—3 carbon atoms or alkyl of 1—3 carbon atoms optionally substituted with one or more of F, Cl, Br or $(CH_2)_pCOR^{10}$ where p is 1, 2, 3 or 4;

R^4 is CO_2H or CO_2R^{11};

R^5, R^6, R^7 and R^8 are independently H, F, Cl, Br, I, CH_3, CF_3, $S(O)_nR^{12}$ or CH_2CH_3, at least two of R^5, R^6, R^7, and R^8 being H;

R^9 and R^{9A} are independently H or alkyl of 1 to 3 carbon atoms;

R^{10} is OH, OCH_3, OCH_2CH_3, NH_2, $NHCH_3$ or $N(CH_3)_2$;

R^{11} is $(CH_2)_{2-4}NR^9R^{9A}$;

R^{12} is alkyl of 1—5 carbon atoms optionally substituted with one or more of F, Cl and Br;

W, Y and Z are independently H, F, Cl, Br, alkyl of 1—5 carbon atoms, NO_2, alkoxy of 1—5 carbon atoms, alkylthio of 1—5 carbon atoms, OH, CF_3 or NH_2;

m is 0 or 1;

n is 0 or 1; and

q is 0, 1 or 2;

or a pharmaceutically suitable salt thereof; with the following provisos:

1) when R^4 is CO_2H, R^1 is phenyl or phenoxy, and R^5, R^7 and R^8 are H, R^6 cannot be Br;

2) R^5, R^6 and R^7 cannot all be H;

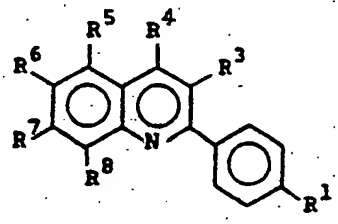
3) when R^4 is $CO_2CH_2CH_2N(CH_3)_2$, R^6 is CH_2CH_3, or R^7 is Cl, R^1 cannot be cyclohexyl;

4) when R^1 is cyclohexyl and R^3 is H, R^6 must be Cl or F, but R^6 and R^8 cannot both be Cl; and

5) when R^1 is 4-$H_2NC_6H_4$ and R^3 is H, R^6 cannot be Cl and R^8 cannot be Br.

PREFERRED EMBODIMENTS

Preferred antitumor compounds have the formula:



(II)

wherein

R^1 is cycloalkyl of 3—7 carbon atoms; phenyl; phenyl substituted with one halogen, alkyl of 1—5 carbon atoms or CF_3; phenoxy; or phenoxy substituted with one halogen or alkyl of 1—5 carbon atoms;

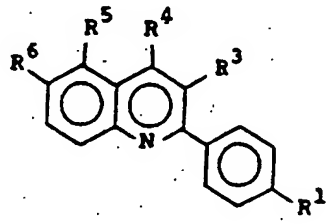
R^3 is H or alkyl of 1—3 carbon atoms;

R^4 is CO_2H or a sodium or potassium salt thereof;

R^5 and R^6 are independently H, halogen, CH_3 of CF_3; and

R^7 and R^8 are independently H or halogen;
or a pharmaceutically suitable salt thereof; with the proviso that:
1) R^5, R^6 and R^7 cannot all be H; and
2) when R^1 is cyclohexyl and R^3 is H, R^6 must be Cl or F, but R^8 and R^8 cannot both be Cl.

More preferred antitumor compounds are compounds which have the formula:



(III)

wherein
R^1 is cyclohexyl, phenyl, phenyl substituted with halogen, phenoxy, or phenoxy substituted with halogen;
R^3 is H or alkyl of 1—3 carbon atoms;
R^4 is CO_2H or a sodium or potassium salt thereof; and
R^5 and R^6 are independently H, halogen or CF_3, provided that both R^5 and R^6 are not H.
Especially preferred are the compounds of Formula III in which:
R^1 is phenyl, phenyl substituted with halogen, phenoxy, or phenoxy substituted with halogen;
R^3 is methyl;
R^5 is H or Cl; and
R^6 is F or Cl.
Specifically preferred for their antitumor activity are:
(1) 2-(1,1'-Biphenyl-4-yl)-6-fluoro-3-methyl-4-quinolinecarboxylic acid, sodium or potassium salt.
(2) 6-Fluoro-3-methyl-2-(4-phenoxyphenyl)-4-quinolinecarboxylic acid, sodium or potassium salt.
(3) 2-(4'-Bromo-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinolinecarboxylic acid, sodium or potassium salt.
(4) 2-(2'-Fluoro-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinolinecarboxylic acid, sodium or potassium salt.
(5) 2-(1,1'-Biphenyl-4-yl)-5-chloro-6-fluoro-3-methyl-4-quinolinecarboxylic acid, sodium or potassium salt.

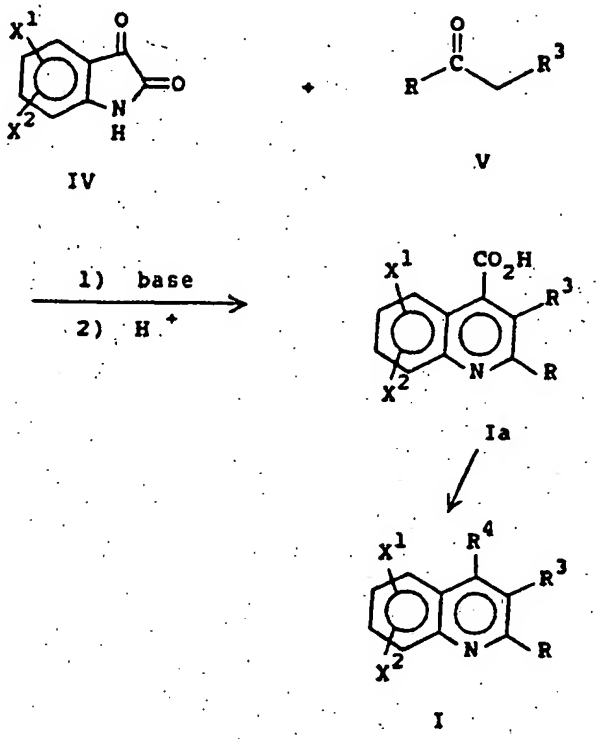
SYNTHESIS

The compounds useful in this invention (Formulae I, II and III) are prepared generally by condensation of an appropriately substituted isatin IV and a ketone V in what is known as the Pfitzinger reaction [Buu-Hoi, N. P.; Royer, R.; Xuong, N. D.; Jucquignon, P.; *J. Org. Chem.*, *18*, 1209 (1953)] to give Ia; then, if desired, further conversion of functional groups on the quinoline provides further compounds of Formula I (Scheme 1). Isatins IV are prepared by the methods described by Papp and references given therein [Papp, F. D.; *Adv. Heterocyclic Chem.*, *18*, 1 (1975)]. The ketones V are prepared by Friedel-Crafts acylation as discussed by House [House, H. O.; *Modern Synthetic Reactions*, 2nd Ed., W. A. Benjamin, 1972, pp. 734ff].

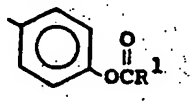
In the following schemes, quinolines bearing up to two unspecified substituents X^1 and X^2 are depicted. The synthetic disclosure is general for quinolines, including all those within the scope of this invention. When certain values of R^5, R^6, R^7 and R^8 are desired, as will be apparent to one skilled in the art, a

protected form of the functional group will be carried through the synthesis, to be deprotected to the desired functional group at a later stage.

Scheme 1



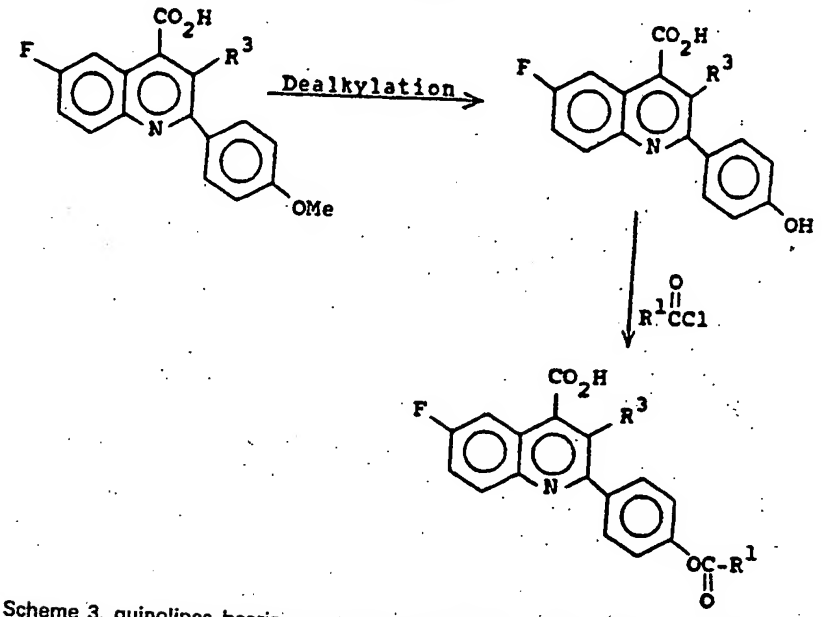
Compounds where R^4 is CO_2H are prepared by reacting the appropriate substituted isatin (IV) with a substituted ketone (V) in a solvent such as ethanol with an aqueous solution of a base such as sodium hydroxide, NH_4OH or potassium hydroxide at a temperature in the range of about 25°C to the boiling point of the solvent used. Acidification of the reaction mixture with a mineral acid such as HCl or an organic acid such as acetic acid provides the quinoline carboxylic acid Ia. Compounds in which R is



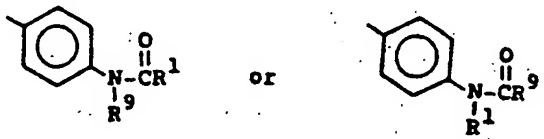
are prepared by acylation of the corresponding hydroxy compound with a carboxylic acid halide such as benzoyl chloride in an inert solvent such as chloroform or a hydrocarbon solvent (benzene) at a temperature in the range of about 0°C to the boiling point of the solvent used, optionally in the presence of a base such as pyridine.

The aforementioned hydroxy compound is prepared from an ether by a dealkylation reaction using BBr_3 or $(CH_3)_3SiI$ in an inert solvent such as dimethylformamide, methylene chloride, or chloroform at a temperature in the range of about 0°C to the boiling point of the solvent used (Scheme 2).

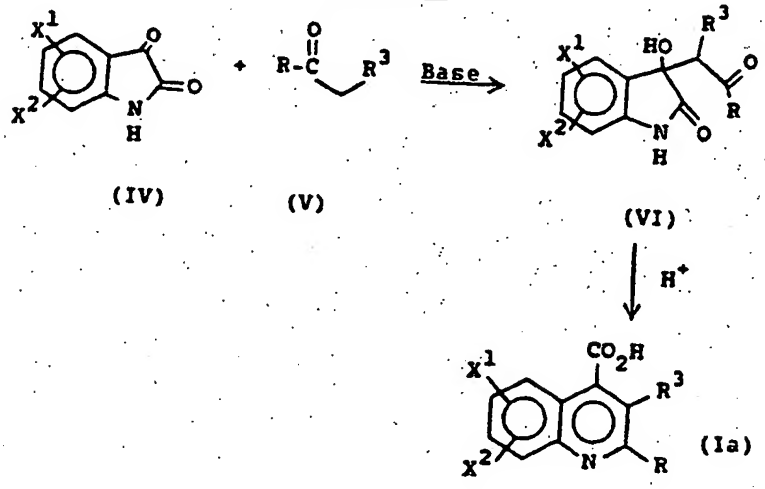
Scheme 2



In Scheme 3, quinolines bearing up to two unspecified substituents X^1 and X^2 are depicted. The synthetic disclosure is general for quinolines, including all those within the scope of this invention. This method is preferred over the Pfitzinger procedure for certain substituents on the isatin (IV) such as X^1 = 4-Cl, or when W, Y or Z are NO_2, or when R is



Scheme 3

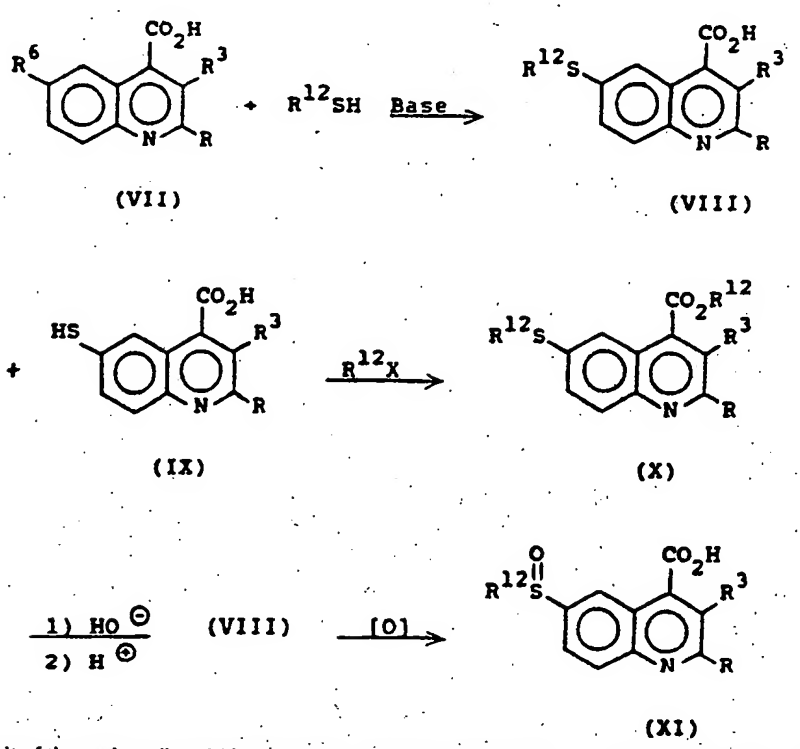


The compounds Ia of Scheme 3 are prepared by reacting the appropriate substituted isatin (IV) with a substituted ketone (V) in a solvent such as ethanol with a base such as diethylamine or triethylamine at a temperature of 25° to 50°C for 2 to 48 hours. Recrystallization of the product (VI) from a solvent is possible although decomposition often occurs. The product (VI) is dissolved in an appropriate solvent such as tetrahydrofuran containing 25—50% by volume of a mineral acid such as hydrochloric acid and heated to a temperature of 50°C to the reflux temperature of the mixture of 2 to 48 hours to provide the quinoline carboxylic acid (Ia).

Quinolinecarboxylic acids such as (VIII) where R^6 is $R^{12}S(O)_n$ are best prepared by reacting the appropriately substituted quinolinecarboxylic acid (VII) where R^6 is F with an appropriate thiolate $R^{12}S^-$ such as MeSK in a solvent such as dimethylformamide at a temperature of 50°C to the reflux temperature of the solvent for 2 to 8 hours (Scheme 4).

It may be necessary, depending upon the reaction conditions chosen, to alkylate the thiol (IX) generated during the reaction by reacting the crude reaction product in an appropriate solvent such as acetone with an alkyl halide $R^{12}X$ such as methyl iodide with or withoiut a base such as potassium carbonate at a temperature of 25°C to the reflux temperature of the solvent for 2 to 24 hours. This gives the corresponding ester (X) which is hydrolyzed by reacting in an appropriate solvent such as ethanol with water and a base such as potassium hydroxide at reflux for 12 to 24 hours to give, after acidification of the reaction mixture with a mineral acid such as HCl, the quinolinecarboxylic acid (VIII). (VIII) can be converted to the corresponding sulfoxide by reacting (VIII) in an appropriate solvent such as ethyl acetate with an oxidizing reagent such as *m*-chloroperoxybenzoic acid at −20° to 25°C for 6 to 24 hours.

Scheme 4

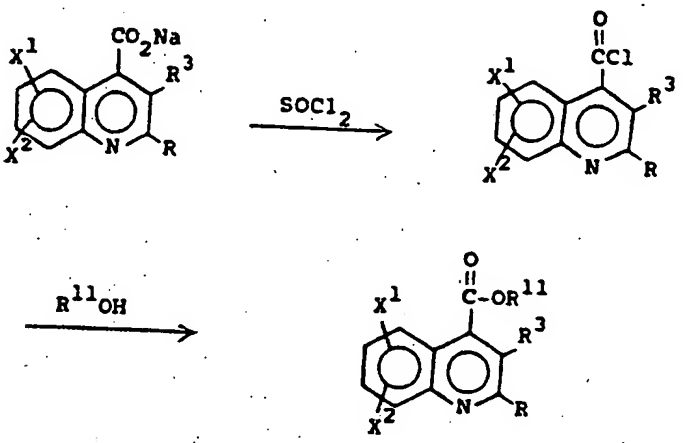


A salt of the carboxylic acid is prepared by dissolving the acid in a protic solvent such as ethanol, and then treating with a metal oxide or hydroxide such as sodium or potassium oxide or hydroxide or an amine such as 1-amino-2-butanol or lysine at a temperature in the range of about 0°C to the boiling point of the solvent used. A salt of an amino group is prepared by dissolving the amine in a solvent such as ethyl ether and adding a mineral acid such as HCl.

A metal salt of a compound of Formula I (e.g., $R^4 = CO_2Na$) can be converted to a corresponding ester in two steps. Conversion of the salt to an acid halide is carried out first by treatment with a reagent such as $SOCl_2$ or oxalyl chloride in an inert solvent such as a hydrocarbon (benzene) at a temperature in the range of about 25°C to the boiling point of the solvent used. This reaction is followed by the addition of an alcohol,

$R^{11}OH$, in a solvent such as tetrahydrofuran at a temperature in the range of 10°C to the boiling point of the solvent used, optionally in the presence of a base such as pyridine, triethylamine, or 4-dimethylamino-pyridine to provide the ester (Scheme 5).

Scheme 5



The invention can be further understood by the following examples in which parts and percentages are by weight unless otherwise indicated; all temperatures are in degrees Centigrade.

Example 1

2-(4-Cyclohexylphenyl)-6-fluoro-3-methylquinoline-4-carboxylic acid

5-Fluoroisatin (100 g, 0.61 mole) and 4-cyclohexylpropiophenone (131 g, 0.61 mole) were suspended in 1100 ml of ethanol and stirred mechanically as a solution of 219 g (5.5 mole) of KOH in 550 ml of water was added dropwise. After the addition was complete, the mixture was heated at reflux for 12 hours, cooled, and the ethanol evaporated under reduced pressure. The resulting solid was dissolved in water and washed with ethyl ether. The aqueous layer was acidified with HCl. The resulting precipitate was filtered and dried. Recrystallization from dimethylformamide and water gave 117 g of 2-(4-cyclohexylphenyl)-6-fluoro-3-methylquinoline-4-carboxylic acid, m.p. 316—323°.

Example 2

2-(4-Biphenylyl)-6-fluoro-3-methylquinoline-4-carboxylic acid

4-Phenylpropiophenone (18.9 g, 0.09 mole) and 5-fluoroisatin (20 g, 0.09 mole) were suspended in 360 ml of ethanol and stirred mechanically as a solution of 35.2 g of KOH in 100 ml water was added dropwise over 15 minutes. The reaction mixture was heated at reflux for 12 hours, cooled, and the ethanol evaporated under reduced pressure. The resulting yellow solid was dissolved in water and washed with ethyl ether. The aqueous layer was cooled to 5° and acidified with glacial acetic acid. The resulting yellow precipitate was filtered and dried. Recrystallization from 200 ml of dimethylformamide and 25 ml water provided 13.8 g of 2-(4-biphenylyl)-6-fluoro-3-methylquinoline-4-carboxylic acid as a white solid, m.p. 303—306°(d).

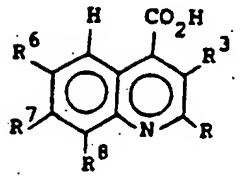
Example 28

2-(2'-Fluoro-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinolinecarboxylic acid

5-Fluoroisatin (72.6 g, 0.44 mole) and 4-(2-fluorophenyl) propiophenone (100 g, 0.44 mole) were suspended in 720 ml of ethanol and stirred mechanically as a solution of KOH (147.8 g, 2.64 mole) in 300 ml of water was added dropwise over 15 minutes. The reaction mixture was heated at reflux for 12 hours, cooled, and the ethanol evaporated under reduced pressure. The resulting solid was dissolved in water and washed with ethyl ether. The aqueous layer was cooled to 5° and acidified with glacial acetic acid. The resulting precipitate was filtered, washed 2 times with 300 ml of ethyl ether and dried. Recrystallization from dimethylformamide and water gave 84 g of a white 2-(2'-Fluoro-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinolinecarboxylic acid, m.p. 315—317°.

The compounds of Examples 1, 2 and 28, other compounds which have been prepared using the procedures described for the compounds of Examples 1, 2 and 28, and other compounds which may be prepared by such procedures, are listed in Table 1.

Table 1



Ex.	R	R^3	R^6	R^7	R^8	m.p.(°C)
1	4-*c*-$C_6H_{11}C_6H_4$	CH_3	F	H	H	316-323
2	4-$C_6H_5C_6H_4$	CH_3	F	H	H	303-306(d)
3	4-*c*-$C_6H_{11}C_6H_4$	CH_3	Cl	H	H	320-322(d)
4	4-*c*-$C_6H_{11}C_6H_4$	H	Cl	H	H	264-265
5	4-*c*-$C_6H_{11}C_6H_4$	H	F	H	H	280-284
6	4-*c*-$C_6H_{11}C_6H_4$	CH_3	CH_3	H	H	308-312(d)
7	4-*n*-$C_{10}H_{21}C_6H_4$	CH_3	F	H	H	256-261
8	4-*n*-$C_6H_{13}C_6H_4$	CH_3	F	H	H	278-285
9	4-$CH_3CH_2(CH_3)CHC_6H_4$	CH_3	F	H	H	290-297
10	4-*c*-$C_6H_{11}C_6H_4$	CH_3CH_2	F	H	H	295-297
11	4-$C_6H_5OC_6H_4$	CH_3	F	H	H	318-320(d)
12	4-(4-BrC_6H_4)C_6H_4	CH_3	F	H	H	318-323(d)
13	4-$(CH_3)_2CHSC_6H_4$	CH_3	F	H	H	280-283
14	4-$C_6H_5C_6H_4$	CH_3	CH_3	H	H	327-329(d)
15	4-*c*-$C_6H_{11}C_6H_4$	CH_3CH_2	CH_3	H	H	290(d)
16	4-$C_6H_5CH_2OC_6H_4$	CH_3	F	H	H	297-302
17	4-$CH_3CH_2(CH_3)CHC_6H_4$	CH_3CH_2	F	H	H	286-291
18	4-$C_6H_5C_6H_4$	CH_3CH_2	F	H	H	274-279(d)
19	4-$C_6H_5C_6H_4$	CH_3	Cl	H	H	302-305
20	4-$C_6H_5OC_6H_4$	CH_3	Cl	H	H	296-301
21	4-$C_6H_5SC_6H_4$	CH_3	Cl	H	H	313-316
22	4-$C_6H_5CH_2C_6H_4$	CH_3	Cl	H	H	265-275
23	4-(4-FC_6H_4)C_6H_4	CH_3	Cl	H	H	319-323
24	4-(4-$CH_3OC_6H_4$)C_6H_4	CH_3	Cl	H	H	310-314
25	4-$(CH_3)_2CHS(O)C_6H_4$	CH_3	F	H	H	

Table 1 (continued)

Ex.	R	R^3	R^6	R^7	R^8	m.p.(°C)
26	4-$C_6H_5CH_2SC_6H_4$	CH_3	F	H	H	281-287
27	4-(4-BrC_6H_4)C_6H_4	CH_3	Cl	H	H	319-324(d)
28	4-(2-FC_6H_4)C_6H_4	CH_3	F	H	H	315-317
29	4-(4-ClC_6H_4O)C_6H_4	CH_3	F	H	H	299-303
30	4-(4-$CH_3C_6H_4$)C_6H_4	CH_3	F	H	H	317-319
31	4-(4-FC_6H_4)C_6H_4	CH_3	F	H	H	310-314
32	4-(4-$CF_3C_6H_4$)C_6H_4	CH_3O	F	H	H	
33	4-$C_6H_5C_6H_4$	H	F	H	H	272-278
34	4-$C_6H_5S(O)C_6H_4$	CH_3	F	H	H	239-247
35	4-(4-FC_6H_4O)C_6H_4	CH_3	F	H	H	291-297
36	4-(3,4-$Cl_2C_6H_3$)C_6H_4	CH_3	F	H	H	315-319
37	4-$C_6H_5C_6H_4$	CH_3O	F	H	H	219-223
38	4-(3-Cl,4-$CH_3C_6H_3$)C_6H_4	CH_3	F	H	H	316-324
39	4-(3,4-$(CH_3)_2C_6H_3$)C_6H_4	CH_3	F	H	H	321-324
40	4-(4-$(CH_3CH_2)C_6H_4$)C_6H_4	CH_3	F	H	H	309-315
41	4-(3-$(CH_3CH_2)C_6H_4$)C_6H_4	CH_3	F	H	H	
42	4-C_6H_5-3-pyridyl	CH_3	F	H	H	
43	4-C_6H_5-2-furanyl	CH_3	F	H	H	
44	4-C_6H_5-2-thienyl	CH_3	F	H	H	345-350
45	4-c-$C_6H_{11}C_6H_4$	CH_3	Br	H	H	325-330
46	4-c-$C_6H_{11}C_6H_4$	CH_3	Br	H	Br	275-280
47	4-$C_6H_5C_6H_4$	CH_3	Cl	Cl	H	
48	4-c-$C_6H_{11}C_6H_4$	CH_3	CF_3	H	H	320-325
49	4-$C_6H_5C_6H_4$	CH_3	H	Cl	H	315-320
50	4-$(C_6H_5O)C_6H_4$	CH_3	H	Cl	H	315-318
51	4-$C_6H_5C_6H_4$	CH_3	CH_3CH_2	H	H	295-300
52	4-$C_6H_5C_6H_4$	CH_3	Br	H	H	313-314
53	4-$(C_6H_5O)C_6H_4$	CH_3	Br	H	H	273-278
54	4-(4-FC_6H_4)C_6H_4	CH_3	F	Cl	H	
55	4-$C_6H_5C_6H_4$	CH_3	H	CH_3	H	324-328
56	4-$C_6H_5C_6H_4$	CH_3	CF_3	H	H	320-323
57	4-$(C_6H_5O)C_6H_4$	CH_3	CF_3	H	H	294-298

Table 1 (continued)

Ex.	R	R^3	R^6	R^7	R^8	m.p.(°C)
58	4-$C_6H_5C_6H_4$	CH_3	CH_3	Cl	H	333-336
59	4-(C_6H_5O)C_6H_4	CH_3	CH_3	Cl	H	314-318
60	4-$C_6H_5C_6H_4$	CH_3	Br	H	Br	270-273
61	4-$C_6H_5C_6H_4$	CH_3	F	Cl	H	327-332
62	4-c-$C_3H_5C_6H_4$	CH_3	F	H	H	
63	4-c-$C_5H_9C_6H_4$	CH_3	F	H	H	
64	4-($C_6H_5(CH_3)N$)C_6H_4	CH_3	F	H	H	
65	4-(C_6H_5CONH)C_6H_4	CH_3	F	H	H	
66	4-($C_6H_5CO_2$)C_6H_4	CH_3	F	H	H	
67	5-C_6H_5-2-imidazoyl	CH_3	F	H	H	
68	(4-C_6H_5,2-CH_3)C_6H_3	CH_3	F	H	H	316-320°
69	4-(2-FC_6H_4), 3-FC_6H_3	CH_3	F	H	H	
70	4-(2-FC_6H_4)C_6H_4	CH_3	Cl	H	H	
71	4-$C_6H_5C_6H_4$	CH_3	I	H	H	325-327
72	4-(4-$CF_3C_6H_4$)C_6H_4	CH_3	F	H	H	
73	4-(3-FC_6H_4)C_6H_4	CH_3	F	H	H	305-310
74	4-(2,4-$F_2C_6H_3$)C_6H_4	CH_3	F	H	H	325-328
75	4-(4-FC_6H_4O)C_6H_4	H	F	H	H	310-315

c-C_6H_{11} = cyclohexyl
c-C_5H_9 = cyclopentyl
c-C_3H_5 = cyclopropyl

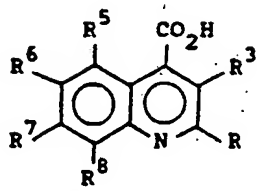
Example 76

2-(4-Biphenyl)-3-methyl-6-methylthio-4-quinoline carboxylic acid

The compound of Example 2, 2-(4-biphenyl)-6-fluoro-3-methyl-4-quinolinecarboxylic acid, (7.2 g, 0.02 mole) and potassium methylmercaptide (6 g) were dissolved in 100 ml of dimethylformamide and warmed at 130° for 3 hours. The mixture was cooled and the solvent evaporated under reduced pressure. The residue was dissolved in 250 ml of H_2O, filtered and the filtrate acidified to pH 2. The yellow precipitate was filtered and dried. A portion of the yellow precipitate (1.8 g, 0.005 mole) was suspended in acetone containing 5 ml of methyl iodide and 4 g of potassium carbonate and was heated to reflux for 24 hours. The reaction mixture was filtered and evaporated at reduced pressure. The residue was dissolved in ethyl ether, washed with H_2O, dried with sodium sulfate and evaporated at reduced pressure to give a solid. The solid obtained in this manner from several batches (6 g) was combined and dissolved in 70 ml of ethanol and 30 ml of H_2O containing 10 g of potassium hydroxide. The mixture was heated at reflux for 12 hours. The mixture was cooled, evaporated at reduced pressure, dissolved in 300 ml of H_2O and washed with ethyl ether. The aqueous solution was acidified to pH 2 with HCl and the precipitate collected, washed with water and hot ethanol to give 4.9 g of 2-(4-Biphenyl)-3-methyl-6-methylthio-4-quinolinecarboxylic acid, m.p. 316—318°(d).

The compound of Example 76 and other compounds which can be prepared using this procedure are listed in Table 2.

Table 2



Ex.	R	R^3	R^5	R^6	R^7	R^8	m.p. (°C)
76	4-$C_6H_5C_6H_4$	CH_3	H	CH_3S	H	H	316-318(d)
77	4-$C_6H_5C_6H_4$	CH_3	H	$CH_3S(O)$	H	H	
78	4-(2-FC_6H_4)C_6H_4	CH_3	H	CH_3S	H	H	
79	4-(4-$CH_3C_6H_4$)C_6H_4	CH_3	H	CH_3S	H	H	

Example 81

2-(4-Biphenyl)-5-chloro-6-fluoro-3-methyl-4-quinolinecarboxylic acid

4-Chloro-5-fluoroisatin (4 g, 0.02 mole), diethylamine (1.46 g, 0.02 mole) and 4-phenylpropiophenone (4.4 g, 0.021 mole) were suspended in 100 ml of ethanol and stirred for 12 hours. The precipitate was filtered, washed with cold ethanol and dried to give 2.1 g of crude adduct (m.p. 202—206°).

This was dissolved in 75 ml of tetrahydrofuran and 30 ml of concentrated HCl. The resulting solution was refluxed for 24 hours, cooled and diluted with H_2O. The tetrahydrofuran was evaporated under reduced pressure. The precipitate was filtered, washed with ether and boiled with methanol to give 0.90 g of 2-(4-biphenyl)-5-chloro-6-fluoro-3-methyl-4-quinolinecarboxylic acid as a crystalline solid, m.p. 300—305°.

Example 86

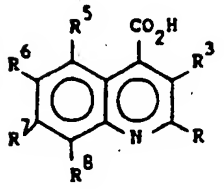
6-Fluoro-3-methyl-2-(4-nitrophenoxyphenyl)-4-quinolinecarboxylic acid

5-Fluoroisatin (2.0 g, 0.0104 mole), diethylamine (0.77 g, 0.0105 mole) and 4-(4-nitrophenoxy)propiophenone (2.82 g, 0.0104 mole) were suspended in 100 ml of ethanol and stirred at 25° for 12 hours. The precipitate was filtered, washed with toluene and air dried to give 3.0 g of crude adduct.

The crude product obtained from two of the above preparations (5.0 g, 0.0108 mole) was combined in 180 ml of tetrahydrofuran and 40 ml of concentrated HCl. The resulting solution was refluxed for 12 hours, cooled and the solvent was evaporated under reduced pressure. The solid residue was washed with ethyl ether and dried to give 4.37 g of 6-fluoro-3-methyl-2-(4-nitrophenoxyphenyl)-4-quinolinecarboxylic acid as a white solid, m.p. 335—337°.

The compounds of Examples 81 and 86, other compounds which have been prepared using the procedures for the compounds of Examples 81 and 86, and other compounds which may be prepared by such procedures, are listed in Table 3.

Table 3



Ex.	R	R^3	R^5	R^6	R^7	R^8	m.p.(°C)
80	4-$C_6H_5C_6H_4$	CH_3	Cl	H	H	H	295-296(d)
81	4-$C_6H_5C_6H_4$	CH_3	Cl	F	H	H	305-308(d)
82	4-$C_6H_5C_6H_4$	CH_3	Cl	H	Cl	H	301-305(d)
83	4-$C_6H_5C_6H_4$	CH_3	Cl	CH_3	H	H	295-298(d)
84	4-(2-FC_6H_4)C_6H_4	CH_3	Cl	F	H	H	300-305
85	4-(4-$CH_3C_6H_4$)C_6H_4	CH_3	Cl	F	H	H	293-296
86	4-(4-$NO_2C_6H_4O$)C_6H_4	CH_3	H	F	H	H	335-337
87	4-$C_6H_5C_6H_4$	CH_3	H	H	F	H	307-311(d)
88	4-(4-$CF_3C_6H_4$)C_6H_4	CH_3CH_2	Cl	F	H	H	
89	4-(3-Cl,4-$CH_3C_6H_3$)C_6H_4	CH_3	Cl	F	H	H	
90	4-(3-Cl,4-$CH_3C_6H_3$)C_6H_4	CH_3	Cl	H	H	H	

Example 91

Sodium 2-(4-Cyclohexylphenyl)-6-fluoro-3-methylquinoline-4-carboxylate

The compound of Example 1 (10.0 g, 0.0275 mole) was suspended in 400 ml of ethanol and treated with 1*N* NaOH (27.5 ml, 0.0275 mole). The mixture was stirred until the solution was clear; the ethanol and water were evaporated at reduced pressure to give 9.95 g of the sodium salt as a white solid, m.p. 350°(d).

Example 92

Sodium 2-(4-Biphenylyl)-6-fluoro-3-methylquinoline-4-carboxylate

The compound of Example 2 (3.57 g, 0.01 mole) was dissolved in 500 ml of ethanol and treated with 1*N* NaOH (10 ml), and heated at reflux for 30 minutes. The ethanol and water were evaporated at reduced pressure to give 3.6 g of the sodium salt as a pale tan solid, m.p. >360°.

Example 118

Sodium 2-(2'-Fluoro-1,1'-biphenyl-4-yl)-6-fluoro-3-methylquinoline-4-carboxylate

The compound of Example 28 (37.5 g, 0.10 mole) was suspended in 1,000 ml of ethanol and treated with 1*N* NaOH (100 ml, 0.10 mole). The mixture was warmed and stirred until clear; the ethanol and water were evaporated at reduced pressure to give 39.6 g of the white solid sodium 2-(2'-fluoro-1,1'-biphenyl-4-yl)-6-fluoro-3-methylquinoline-4-carboxylate, m.p. >360°.

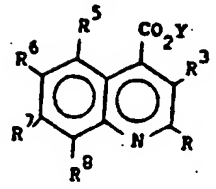
Example 164

Sodium 2-(4-Biphenylyl)-5-chloro-6-fluoro-3-methylquinoline-4-carboxylate

The compound of Example 81 (7.85 g, 0.02 mole) was suspended in 150 ml of water and treated with 1*N* NaOH (19.9 ml, 0.0199 mole), and 150 ml of ethanol was added. The mixture was stirred until the solution was clear and filtered to remove any insoluble material. The ethanol and water were removed at reduced pressure to give 8.1 g of the white solid sodium salt, m.p. >360°.

The compounds of Examples 91, 92, 118 and 164, other compounds which have been prepared by the procedures given above, and other compounds which can be prepared using such procedures are listed in Table 4.

Table 4



Ex.	R	R^3	R^5	R^6	R^7	R^8	Y	m.p. (°C)
91	4-c-$C_6H_{11}C_6H_4$	CH_3	H	F	H	H	Na	350(d)
92	4-$C_6H_5C_6H_4$	CH_3	H	F	H	H	Na	>360
93	4-c-$C_6H_{11}C_6H_4$	CH_3	H	Cl	H	H	Na	>350
94	4-c-$C_6H_{11}C_6H_4$	H	H	Cl	H	H	Na	>350
95	4-c-$C_6H_{11}C_6H_4$	H	H	F	H	H	Na	>350
96	4-c-$C_6H_{11}C_6H_4$	CH_3	H	CH_3	H	H	Na	342-351
97	4-n-$C_{10}H_{21}C_6H_4$	CH_3	H	F	H	H	Na	332-335
98	4-n-$C_6H_{13}C_6H_4$	CH_3	H	F	H	H	Na	
99	4-$CH_3CH_2(CH_3)CHC_6H_4$	CH_3	H	F	H	H	Na	340-345
100	4-c-$C_6H_{11}C_6H_4$	CH_3CH_2	H	F	H	H	Na	>350
101	4-$C_6H_5OC_6H_4$	CH_3	H	F	H	H	Na	>350
102	4-(4-BrC_6H_4)C_6H_4	CH_3	H	F	H	H	Na	>350
103	4-$(CH_3)_2CHSC_6H_4$	CH_3	H	F	H	H	Na	339-343
104	4-$C_6H_5C_6H_4$	CH_3	H	CH_3	H	H	Na	>350
105	4-c-$C_6H_{11}C_6H_4$	CH_3CH_2	H	CH_3	H	H	Na	>350
106	4-$C_6H_5CH_2OC_6H_4$	CH_3	H	F	H	H	Na	>350
107	4-$CH_3CH_2(CH_3)CHC_6H_4$	CH_3CH_2	H	F	H	H	Na	302-306
108	4-$C_6H_5C_6H_4$	CH_3CH_2	H	F	H	H	Na	>350
109	4-$C_6H_5C_6H_4$	CH_3	H	Cl	H	H	Na	>350
110	4-$C_6H_5OC_6H_4$	CH_3	H	Cl	H	H	Na	170-175
111	4-$C_6H_5SC_6H_4$	CH_3	H	Cl	H	H	Na	319-324
112	4-$C_6H_5CH_2C_6H_4$	CH_3	H	Cl	H	H	Na	305-315
113	4-(4-FC_6H_4)C_6H_4	CH_3	H	Cl	H	H	Na	>350
114	4-(4-$CH_3OC_6H_4$)C_6H_4	CH_3	H	Cl	H	H	Na	>360
115	4-$(CH_3)_2CHS(O)C_6H_4$	CH_3	H	F	H	H	Na	

Table 4 (continued)

Ex.	R	R^3	R^5	R^6	R^7	R^8	Y	m.p. (°C)
116	4-$C_6H_5CH_2SC_6H_4$	CH_3	H	F	H	H	Na	
117	4-(4-BrC_6H_4)C_6H_4	CH_3	H	Cl	H	H	Na	>360
118	4-(2-FC_6H_4)C_6H_4	CH_3	H	F	H	H	Na	>360
119	4-(4-ClC_6H_4O)C_6H_4	CH_3	H	F	H	H	Na	>350
120	4-(4-$CH_3C_6H_4$)C_6H_4	CH_3	H	F	H	H	Na	>350
121	4-(4-FC_6H_4)C_6H_4	CH_3	H	F	H	H	Na	>360
122	4-(4-$CF_3C_6H_4$)C_6H_4	CH_3O	H	F	H	H	Na	
123	4-$C_6H_5C_6H_4$	H	H	F	H	H	Na	>360
124	4-$C_6H_5S(O)C_6H_4$	CH_3	H	F	H	H	Na	251-260
125	4-(4-FC_6H_4O)C_6H_4	CH_3	H	F	H	H	Na	
126	4-(3,4-$Cl_2C_6H_3$)C_6H_4	CH_3	H	F	H	H	Na	338-351
127	4-$C_6H_5C_6H_4$	CH_3O	H	F	H	H	Na	345-349
128	4-(3-Cl,4-$CH_3C_6H_3$)C_6H_4	CH_3	H	F	H	H	Na	>360
129	4-(3,4-$(CH_3)_2C_6H_3$)C_6H_4	CH_3	H	F	H	H	Na	>350
130	4-(4-(CH_3CH_2)C_6H_4)C_6H_4	CH_3	H	F	H	H	Na	>360
131	4-(3-(CH_3CH_2)C_6H_4)C_6H_4	CH_3	H	F	H	H	Na	
132	4-C_6H_5-3-pyridyl	CH_3	H	F	H	H	Na	
133	4-C_6H_5-2-furanyl	CH_3	H	F	H	H	Na	
134	4-C_6H_5-2-thienyl	CH_3	H	F	H	H	Na	>360
135	4-c-$C_6H_{11}C_6H_4$	CH_3	H	Br	H	H	Na	>360
136	4-c-$C_6H_{11}C_6H_4$	CH_3	H	Br	H	Br	Na	298-300(d)
137	4-$C_6H_5C_6H_4$	CH_3	H	Cl	Cl	H	Na	
138	4-c-$C_6H_{11}C_6H_4$	CH_3	H	CF_3	H	H	Na	
139	4-$C_6H_5C_6H_4$	CH_3	H	H	Cl	H	Na	>360
140	4-(C_6H_5O)C_6H_4	CH_3	H	H	Cl	H	Na	
141	4-$C_6H_5C_6H_4$	CH_3	H	CH_3CH_2	H	H	Na	>360
142	4-$C_6H_5C_6H_4$	CH_3	H	Br	H	H	Na	>360
143	4-(C_6H_5O)C_6H_4	CH_3	H	Br	H	H	Na	228
144	4-(4-FC_6H_4)C_6H_4	CH_3	H	F	Cl	H	Na	
145	4-$C_6H_5C_6H_4$	CH_3	H	H	CH_3	H	Na	>350
146	4-$C_6H_5C_6H_4$	CH_3	H	CF_3	H	H	Na	>360
147	4-(C_6H_5O)C_6H_4	CH_3	H	CF_3	H	H	Na	338-342

Table 4 continued

Ex.	R	R^3	R^5	R^6	R^7	R^8	Y	m.p.(°C)
148	4-$C_6H_5C_6H_4$	CH_3	H	CH_3	Cl	H	Na	>360
149	4-$(C_6H_5O)C_6H_4$	CH_3	H	CH_3	Cl	H	Na	318-320
150	4-$C_6H_5C_6H_4$	CH_3	H	Br	H	Br	Na	340-345
151	4-$C_6H_5C_6H_4$	CH_3	H	F	Cl	H	Na	>360
152	4-c-$C_3H_5C_6H_4$	CH_3	H	F	H	H	Na	
153	4-c-$C_5H_9C_6H_4$	CH_3	H	F	H	H	Na	
154	4-$(C_6H_5(CH_3)N)C_6H_4$	CH_3	H	F	H	H	Na	
155	4-$(C_6H_5CONH)C_6H_4$	CH_3	H	F	H	H	Na	
156	4-$(C_6H_5CO_2)C_6H_4$	CH_3	H	F	H	H	Na	
157	4-C_6H_5-2-imidazoyl	CH_3	H	F	H	H	Na	
158	4-C_6H_5,2-$CH_3C_6H_3$	CH_3	H	F	H	H	Na	>360
159	4-(2-FC_6H_4),3-FC_6H_3	CH_3	H	F	H	H	Na	
160	4-(2-FC_6H_4)C_6H_4	CH_3	H	Cl	H	H	Na	
161	4-$C_6H_5C_6H_4$	CH_3	H	CH_3S	H	H	Na	>350
162	4-$C_6H_5C_6H_4$	CH_3	H	$CH_3S(O)$	H	H	Na	
163	4-$C_6H_5C_6H_4$	CH_3	Cl	H	H	H	Na	>360
164	4-$C_6H_5C_6H_4$	CH_3	Cl	F	H	H	Na	>360
165	4-$C_6H_5C_6H_4$	CH_3	Cl	H	Cl	H	Na	>350
166	4-$C_6H_5C_6H_4$	CH_3	Cl	CH_3	H	H	Na	>340
167	4-(2-FC_6H_4)C_6H_4	CH_3	Cl	F	H	H	Na	330-335(d)
168	4-(4-$CH_3C_6H_4$)C_6H_4	CH_3	Cl	F	H	H	Na	>345
169	4-c-$C_6H_{11}C_6H_4$	CH_3	H	F	H	H	K	350-360(d)
170	4-$C_6H_5C_6H_4$	CH_3	H	F	H	H	K	>350
171	4-$C_6H_5C_6H_4$	CH_3	H	Cl	H	H	K	>350
172	4-$(C_6H_5O)C_6H_4$	CH_3	H	Cl	H	H	K	164-171
173	4-$(C_6H_5S)C_6H_4$	CH_3	H	Cl	H	H	K	310-325
174	4-(4-BrC_6H_4)C_6H_4	CH_3	H	F	H	H	K	370
175	4-(4-BrC_6H_4)C_6H_4	CH_3	H	Cl	H	H	K	>360
176	4-(2-FC_6H_4)C_6H_4	CH_3	H	F	H	H	K	339-346
177	4-(4-FC_6H_4)C_6H_4	CH_3	H	F	H	H	K	270-275

Table 4 continued

Ex.	R	R^3	R^5	R^6	R^7	R^8	Y	m.p. (°C)
178	4-$C_6H_5C_6H_4$	CH_3	H	F	H	H	lysine	222-231
179	4-$C_6H_5C_6H_4$	CH_3	H	F	H	H	1-amino-2-butanol	128-134
180	4-*n*-$C_6H_{13}C_6H_4$	CH_3	H	F	H	H	lysine	205-212
181	4-*c*-$C_6H_{11}C_6H_4$	CH_3	H	F	H	H	lysine	226-231
182	4-$C_6H_5C_6H_4$	H	H	F	H	H	K	326-329
183	4-(4-BrC_6H_4)C_6H_4	CH_3	H	F	H	H	lysine	253-258
184	4-(4-$NO_2C_6H_4O$)C_6H_4	CH_3	H	F	H	H	Na	>360
185	4-$C_6H_5C_6H_4$	CH_3	H	I	H	H	Na	>360
186	4-$C_6H_5C_6H_4$	CH_3	H	H	F	H	Na	360
187	4-(4-FC_6H_4O)C_6H_4	H	H	F	H	H	Na	
188	4-(2,4-$F_2C_6H_3$)C_6H_4	CH_3	H	F	H	H	Na	
189	4-(2-FC_6H_4)C_6H_4	CH_3	Cl	F	H	H	Na	330-335(d)
190	4-(3-FC_6H_4)C_6H_4	CH_3	H	H	H	H	Na	>360
191	4-(4-HOC_6H_4)C_6H_4	CH_3	H	F	H	H	Na	>360

lysine = $H_3\overset{+}{N}CH_2CH_2CH_2CH_2\underset{NH_2}{\underset{|}{C}}HCO_2H$

1-amino-2-butanol = $H_3\overset{+}{N}CH\underset{OH}{\underset{|}{C}}HCH_2CH_3$

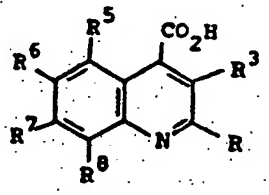
Example 192

6-Chloro-2-(4'-hydroxy-1,1'-biphenyl-4-yl)-3-methyl-4-quinolinecarboxylic acid

The compound of Example 24 (4.0 g, 0.01 mole) was added in portions to a solution of borontribromide (5.7 ml, 0.06 mole) in 90 ml of chloroform at 25° under nitrogen. This maroon suspension was stirred for 1 hour then poured onto wet ice. The resulting yellow precipitate was filtered, washed with chloroform and air dried. The solid was dissolved in 1*N* NaOH, washed with chloroform and then acidified with glacial acetic acid to give a yellow precipitate which was filtered and air dried to give 4.2 g of the yellow solid 6-chloro-2-(4'-hydroxy-1,1'-biphenyl-4-yl)-3-methyl-4-quinolinecarboxylic acid, m.p. >360°.

The compound of Example 192 and other compounds which can be prepared using such procedures are listed in Table 5.

Table 5



Ex.	R	R^3	R^5	R^6	R^7	R^8	m.p. (°C)
192	4-(4-HOC_6H_4)C_6H_4	CH_3	H	F	H	H	>360
193	4-(4-HOC_6H_4)C_6H_4	CH_3	H	F	H	H	
194	4-(4-HOC_6H_4)C_6H_4	CH_3	Cl	F	H	H	

Utility

Results of the various biological tests described below establish that the compounds of this invention have the property of inhibiting not only the growth of transplanted mouse tumors but also the growth of human tumors implanted in mice.

The efficacy of the compounds of this invention against the transplanted mouse tumors was evaluated in test systems currently in use at the National Cancer Institute for the detection and assessment of anticancer activity. Most clinically effective drugs exhibit activity in these tests and the tests have a good record of predicting clinical efficacy [Goldin, A., Venditti, J. M. MacDonald, J. S., Muggia, F. M., Henney, J. E. and V. T. Devita, Jr., *Europ. J. Cancer, 17,* 129—142, (1981); Venditti, J. M., *Seminars in Oncology, 8* (4) (1981); Goldin, A. and J. M. Venditti, in *Recent Results in Cancer Research, 70,* S. K. Carter and Y. Sakurai, Eds., Springer-Verlag, Berlin/Heidelberg, 1980].

Melanotic Melanoma B16 Test

The animals used were $B_6C_3F_1$ mice, all of one sex, weighing a minimum of 18 g for males and 17 g for females and all within a 4 g weight range at the start of the test. The test group comprised 9 or 10 mice. The tumor was implanted in each of the test mice by the subcutaneous injection of 0.5 ml of a tumor homogenate prepared by homogenizing a 1 g portion of melanotic melanoma in 10 ml of cold physiological saline. The test compounds suspended in hydroxypropylcellulose were administered intraperitoneally at various doses once daily for nine consecutive days starting on day one relative to the day of tumor inoculation (day 0). The control mice received injections of hydroxypropylcellulose vehicle only. The mice were weighed and survivors were recorded on a regular basis for 60 days. The median survival times and the ratio of the median survival times for treated (T) to control (C) mice were calculated. The median survival time of the nontreated tumored mice ranged from 15 to 17 days. Drug effectiveness was assessed on the basis of the survival time. Results were expressed as a percentage of the control survival time (Survival Time T/C × 100%). The criterion for effectiveness was determined by: T/C × 100 ≥ 125 percent.

Results with the compound of Example 1 and cis-platin, a drug used clinically, are shown in Table 6. The data indicate that the compound of Example 1 is effective against the B16 melanoma in mice.

Table 6

Melanotic Melanoma B16 Test

Compound	Dose (mg/kg)	T/C x 100 (percent) 2 Tests
Example 1	400	131, 179
	200	145, 150
	100	145, 155
	50	148, 138
	25	127, 125
Cisplatin	2	212, 136
	1	- , 175

Lymphoid Leukemia L1210

The animals used in this test were CD_2F_1 mice, all males weighing a minimum of 18 g and all within a 4 g weight range at the start of the test. The test group group consisted of six mice. The tumor was implanted in each of the test mice by the intraperitoneal injection of 0.1 ml of diluted ascitic fluid containing 10^5 cells drawn from a mouse with L1210 leukemia. The test compounds were suspended in hydroxypropylcellulose or saline with Tween® 80 surfactant or dissolved in saline and injected intraperitoneal, at various doses, once daily for nine consecutive days starting on day one relative to the day of tumor inoculation (day 0). The control mice received injections of saline or hydroxypropylcellulose vehicle only. The mice were weighed and survivors were recorded on a regular basis for 30 days. The median survival time and the ratio of the median survival time for treated (T) and control (C) mice was calculated. The median survival time of the non-treated tumored mice ranged from 8—9 days. Drug effectiveness was assessed on the basis of the survival time. Results were expressed as a percentage of the control survival time (Median Survival Time T/C × 100%). The criterion for effectiveness was determined by: T/C × 100 ≥ 125 percent.

Results of tests with compounds of this invention are shown in Table 7. The data indicate that the compounds of the invention are effective against the L1210 leukemia in mice.

Human Colon Tumor Test in vitro

The compounds of this invention were also tested for their ability to inhibit the growth of human colon carcinoma cells *in vitro*. Compounds effective in inhibiting the growth of these cells also show activity in inhibiting the L1210 leukemia in mice.

The human colon carcinoma cells, designated HCT-15, were derived from a specimen of an adenocarcinoma of human colon removed during surgery. The cells were grown in Roswell Park Medical Institute (RPMI) Medium 1640 supplemented with 10% heat inactivated fetal calf serum, penicillin (100 units/ml), streptomycin (100 µg/ml), gentamicin (20 µg/ml), fungizone (25 µg/ml), 0.075 percent sodium bicarbonate, 10 µM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid and 10 µM N-tris(hydroxymethyl)methylglycine. To determine the potency of the test compounds in inhibiting the growth of the cells, the procedure was as follows: on day 0, replicate 35 mm tissue culture dishes were each inoculated with 1.5×10^5 HCT-15 cells in 2 ml supplemented RPMI Medium 1640. On day 1 cells from sample dishes were harvested using trypsin (0.25%) treatment and counted with a hemocytometer to determine the number of cells per dish at the time of the addition of the compounds. Compounds of this invention were added in varying concentrations to other cultures. On day 4, treated and control cultures were harvested by trypsin treatment and the number of cells was determined. The number of doublings for the control cells was determined from the cell numbers on days 1 and 4. The ID_{50}, the concentration of compound required to inhibit by 50 percent the number of doublings, was then calculated from the dose-response curve in which cell numbers were plotted on log-log paper against compound concentrations in micrograms per ml. Results of tests with compounds of this invention and with reference drugs used clinically are shown in Table 7. They show that the compounds are active in inhibiting the growth of the human colon tumor cells.

Table 7

Example No.	L1210 Leukemia (dose in mg/kg) %T/C	in vitro HCT-15 ID50 µg/ml
1	(200) 189	0.05
2	(50) 186	0.10
3	(400) 207	0.50
4	(200) 128	0.48
5	(400) 141	0.02
6	(400) 162	0.24
7	(200) 136	2.30
8	(400) 147	0.40
9	(200) 127	0.07
10	(200) 163	0.03
11	(25) 176	0.19
12	(50) 261	1.00
13	(400) 129	0.24
14	(50) 195	0.38
15	(200) 158	0.28
16	(400) 190	1.00
17	(400) 136	0.65
18	(100) 185	<0.50
19	(25) 234	<0.50
20	(200) 211	<0.50
21	(200) 160	<5.0 and >0.5
22	(100) 135	<5.0 and >0.5
23	(25) 159	<5.0 and >0.5
24	(400) 154	0.28
26	(300) 136	<0.50
27	(50) 155	NT
28	(18) 174	<0.50
29	(18) 194	<0.50
30	(300) 291	<0.50
31	(37.5) 218	<0.50

Table 7 continued

Example No.	L1210 Leukemia (dose in mg/kg) %T/C	*in vitro* HCT-15 ID50 µg/ml
32	(175) 153	<5.0 and >0.5
33	(200) 170	<0.50
34	(400) 170	NT
35	(150) 204	NT
36	(75) 185	NT
37	(50) 155	NT
38	NT	>1
39	NT	<0.1
40	NT	>1
45	(400) 160	0.13
46	NT	0.42
47	NT	3.20
48	NT	0.10
49	(200) 174	>5.00
50	(100) 131	>5.00
51	(75) 173	<0.50
52	(75) 189	<0.50
53	(75) 136	<0.50
54	(300) 125	<0.50
55	(150) 156	<5.0 and >0.5
56	(75) 176	<0.50
57	(150) 197	<0.50
58	(150) 141	>0.50
59	(300) 152	>5.00
60	(300) 192	<0.50
61	(75) 160	NT
68	NT	<1 and >0.1
71	NT	<1.0 and >0.1
73	NT	<0.1
74	(50) 104	NT

Table 7 continued

Example No.	L1210 Leukemia (dose in mg/kg) %T/C	in vitro HCT-15 ID50 µg/ml
75	(150) 145	NT
76	NT	<1.0 and >0.1
80	(25) 128	<0.50
81	(25) 191	<0.50
82	NT	>1.00
83	NT	>1.00
84	NT	<0.1
85	NT	<1 and >0.1
86	(175) 153	<5.0 and >0.50
87	(100) 146	<0.50
91	(100) 103 ♦ (40) 140*	0.04
92	(50) 180, 176, 172	0.03
93	(50) 101♦	0.06, 0.04
94	(100) 107♦	0.65
95	(100) 108♦	0.04
96	(37.5) 97♦	<0.50
97	(25) 110♦	0.14
99	(50) 101♦	0.07, 0.34
100	(50) 103♦	0.028, 0.24
101	(50) 154, 161	0.41
102	(12.5) 164	1.0, 1.9
103	(200) 108♦	0.17
104	(100) 137,164	0.22
105	(12.5) 108♦	0.33
106	(25) 107♦	1.20
107	(25) 116♦	0.09
108	(100) 166	0.10
109	(100) 172	<0.50
110	(25) 135	<0.50
111	(25) 125, 135	<0.50

Table 7 continued

Example No.	L1210 Leukemia (dose in mg/kg) %T/C	*in vitro* HCT-15 ID50 µg/ml
112	(25) 128	<0.50
113	(25) 166, 166	<5.0 and >0.5
114	(50) 121*	1.30
116	(75) 102*	<0.50
117	(25) 163, 175	<5.0 and >0.5
118	(25) 179, 195	0.017
119	(18) 170	<0.50
120	(100) 132	<0.50
121	(18) 175	<0.50
122	(175) 153	<5.0 and >0.5
123	(21.9) 145	<0.50
124	(360) 184	NT
125	(150) 150	NT
126	(37.5) 150	NT
127	(50) 193	NT
128	NT	>1
129	NT	<0.1
134	(100) 110*	<1 and >0.1
135	(400) 160	0.13, 0.55
136	(25) 103*	>0.50
137	(50) 107*	>5.00
139	(100) 146	<5.00
141	(75) 139	<0.50
142	(37.5) 169	<0.50
143	(37.5) 132	<0.50
144	(37.5) 123*	<0.50
145	(75) 132	<0.50
146	(37.5) 164	<0.50
147	(18) 132	<0.50
148	(37.5) 102*	>5.00

Table 7 continued

Example No.	L1210 Leukemia (dose in mg/kg) %T/C	in vitro HCT-15 ID50 µg/ml
149	(75) 107*	>5.00
150	(37.5) 105*	<0.50
151	(75) 144	<5.0 and >0.5
158	NT	<1 and >0.1
161	(100) 148	>1.00
163	(43.8) 180	<0.50
164	(22.5) 234	<0.50
165	NT	>1.00
166	NT	<1.0 and >0.1
167	(12.5) 197	<0.1
169	NT	0.04
170	(25) 188	0.10
171	(100) 164	<0.50
172	(100) 151	<0.50
173	(25) 122	<0.50
174	(12.5) 156, 159	<5 and >0.5
175	(12.5), 156, 159	<5.0 and >0.5
176	(37) 175	<0.50, 0.41
177	(37.5) 172	<0.50
178	(75) 172	<0.50
179	(37.5) 166	<0.50
180	(18) 101*	<0.50
181	(37.5) 108*	<0.50
182	(46) 168	<0.50
183	(22.5) 208	<5.0 and >0.5
184	(175) 153	<5.0 and >0.5
185	(50) 175	<1.0 and >0.1
186	(45) 123	<0.50
187	(75) 131	<0.50
188	(12.5) 187	<0.01

Table 7 continued

Example No.	L1210 Leukemia (dose in mg/kg) %T/C	in vitro HCT-15 ID50 µg/ml
189	(12.5) 197	<0.1
192	(200) 166	>1
Adriamycin	NT	0.01
Cisplatin	NT	0.66
5-Fluorouracil	NT	0.27

* Dosing Q3DX9 instead of Q1DX9

= Compounds dosed at non-optimal Q1DX9 instead of Q3DX9, should be active if dosed Q3DX9.

NT = not tested

The compounds of Examples 1 and 91 were also tested for effectiveness against a human colon tumor implanted in athymic mice. These mice are immunodeficient and thus do not reject implanted tumors of human origin.

Human Colon Tumor HCT—15

The animals used were Swiss NU/NU athymic mice, weighing 20—22 g each at the start of the test. The test group consisted of twelve mice, seven males and five females. The HCT—15 tumor cell line, derived from a patient with adenocarcinoma of the colon, was maintained in culture. The tumor was implanted in each of the test mice by the subcutaneous injection in the flank region of 0.2 ml of physiological saline containing 10^7 HCT—15 cultured cells. Tumors appeared within 72 hours and treatment started one week after tumor inoculation.

Test compounds, suspended in methocel (0.5% in water) or dissolved in water, were injected intraperitoneally once daily for five consecutive days starting on day seven relative to the day of tumor inoculation (day 0). The body weight and the size of the tumor were determined daily. Tumor size was determined by two-dimensional caliper measurements. Tumor weight was estimated from the formula:

$$\frac{1 \times w^2}{2}$$

= mg tumor weight in which 1 = length and w = width of the tumor in mm. The net tumor weight was determined by subtracting from the actual tumor weight at the time of evaluation the initial estimated tumor weight at the time treatment was started (day 7). Drug effectiveness was assessed on the basis of inhibition of the gain in net tumor weight in the treated (T) compared to that of the control (C) mice. Percent tumor growth inhibition was calculated by the formula:

$$\text{Percent tumor growth inhibition} = 1 - \left[\frac{\text{net tumor weight:Treated}}{\text{net tumor weight:Control}}\right] \times 100\%$$

Results of a test are shown in Table 8. The data indicate that the compounds of this invention inhibited the growth of the HCT—15 human colon tumor in mice. 5-Fluorouracil used as a reference drug was toxic at the 40 mg/kg dose and ineffective at the 20 mg/kg dose. 5-Fluorouracil is sometimes used in the treatment of colon tumors in man but is not consistently effective.

Table 8

Human Colon Tumor HCT-15 In Mice

Compound	Dose mg/kg	Day 7* Average Tumor Weight (mg)	Day 21 Average Tumor Weight (mg)	Day 21 Net Tumor Weight gain (mg)	Day 21 Tumor Growth Inhibition (Percent)
Methocel Control	0	56.2	349.9	293.7	0
Example 1	200	56.8	156.3	99.4	66.2
	100	56.6	212.9	156.3	46.8
	50	56.3	252.9	196.6	33.1
Example 91	40	56.8	256.9	200.1	32.0
	20	56.2	245.1	188.9	35.7
	10	56.8	322.8	266.0	10.0
5-Fluorouracil	40		Toxic		
	20	56.7	421.7	365	0

*Day treatment was started.

In summary, tests have shown that the compounds of this invention have antitumor activity against transplanted mouse tumors including the L1210 lymphoid leukemia and the B16 melanotic melanoma, in mice. The compounds are also active against the human colon tumor HCT—15 in tissue culture or xenografted in athymic mice.

Dosage Forms

The antitumor compounds (active ingredients) of this invention can be administered to inhibit tumors by any means that produces contact of the active ingredient with the agent's site of action in the body of a mammal. They can be administered by any conventional means available for use in conjunction with pharmaceuticals; either as individual therapeutic active ingredients or in a combination of therapeutic active ingredients. They can be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will be a tumor-inhibiting amount of active ingredient and will, of course, vary depending upon known factors such as the pharmacodynamic characteristics of the particular active ingredient, and its mode and route of administration; age, health, and weight of the recipient; nature and extent of symptoms, kind of concurrent treatment, frequency of treatment, and the effect desired. Usually a daily dosage of active ingredient can be about 5 to 400 milligrams per kilogram of body weight. Ordinarily 10 to 200, and preferably 10 to 50 milligrams per kilogram per day given in divided doses 2 to 4 times a day or in sustained release form is effective to obtain desired results.

Dosage forms (compositions) suitable for internal administration contain from about 1.0 milligram to about 500 milligrams of active ingredient per unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5—95% by weight based on the total weight of the composition.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions, it can also be administered parenterally, in sterile liquid dosage forms.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, sucrose, mannitol, starch, cellulose derivatives, magnesium stearate and stearic acid. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar

coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol of polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration contain preferably a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffers substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid either alone or combined are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in *Remington's Pharmaceutical Sciences,* A. Osol, a standard reference text in this field.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 175 milligrams of lactose, 24 milligrams of talc, and 6 milligrams magnesium stearate.

A mixture of active ingredient in soybean oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of cornstarch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Injectable

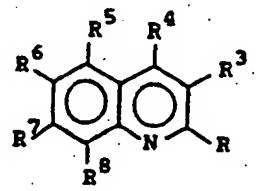
A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution is made isotonic with sodium chloride and sterilized.

Suspension

An aqueous suspension is prepared for oral administration so that each 5 milliliters contain 100 milligrams of finely divided active ingredient, 200 milligrams of sodium carboxymethyl cellulose, 5 milligrams of sodium benzoate, 1.0 grams of sorbitol solution, U.S.P, and 0.025 milliliters of vanillin.

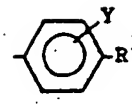
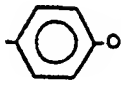
Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

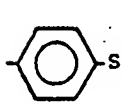
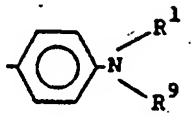
1. An antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound having the formula:

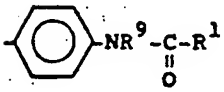
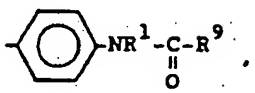


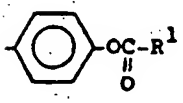
(I)

wherein

R is  .  .

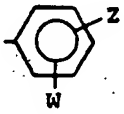
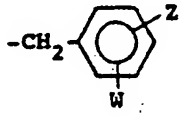
 .  .

 .  .

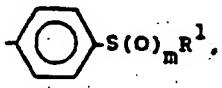
 . or  :

X is O, $S(O)_q$, NH or CH=N;

R^1 is $CH_3CH_2(CH_3)CH$, alkyl of 5—12 carbon atoms, alkenyl of 5—12 carbon atoms, cycloalkyl of 3—7 carbon atoms, cycloalkylalkyl of 5—12 carbon atoms, cycloalkenyl of 5—7 carbon atoms.

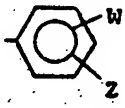
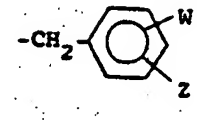
 or  .

when R is

 .

R^1 can be in addition alkyl of 3—4 carbon atoms;

R^2 is

 or  :

R^3 is H, alkoxy of 1—3 carbon atoms, alkylthio of 1—3 carbon atoms or alkyl of 1—3 carbon atoms optionally substituted with one or more of F, Cl, Br or $(CH_2)_pCOR^{10}$ where p is 1, 2, 3 or 4;

R^4 is CO_2H or CO_2R^{11};

R^5, R^6, R^7 and R^8 are independently H, F, Cl, Br, I, CH_3, CF_3, $S(O)_nR^{12}$ or CH_2CH_3, at least two of R^5, R^6, R^7 and R^8 being H;

R^9 and R^{9A} are independently H or alkyl of 1 to 3 carbon atoms;

R^{10} is OH, OCH_3, OCH_2CH_3, NH_2, $NHCH_3$ or $N(CH_3)_2$;

R^{11} is $(CH_2)_{2-4}NR^9R^{9A}$;

R^{12} is alkyl or 1—5 carbon atoms optionally substituted with one or more of F, Cl and Br;

W, Y and Z are independently H, F, Cl, Br, alkyl of 1—5 carbon atoms, NO_2, alkoxy of 1—5 carbon atoms, alkylthio of 1—5 carbon atoms, OH, CF_3 or NH_2;

m is 0 or 1;

n is 0 or 1; and

q is 0, 1 or 2;

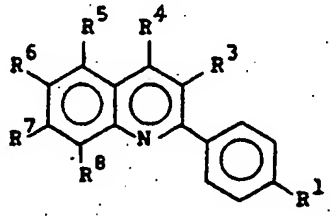
or a pharmaceutically suitable salt thereof; with the following provisos:

1) R^5, R^6 and R^7 cannot all be H;

2) when R^4 is $CO_2CH_2CH_2N(CH_3)_2$, R^8 is CH_2CH_3, or R^7 is Cl, R^1 cannot be cyclohexyl; and

3) when R^1 is cyclohexyl and R^3 is H, R^6 must be Cl or F, but R^6 and R^8 cannot both be Cl.

2. An antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound having the formula:



(II)

wherein

R^1 is cycloalkyl of 3—7 carbon atoms; phenyl; phenyl substituted with one halogen, alkyl of 1—5 carbon atoms or CF_3; phenoxy; or phenoxy substituted with one halogen or alkyl of 1—5 carbon atoms;

R^3 is H or alkyl of 1—3 carbon atoms;

R^4 is CO_2H or a sodium or potassium salt thereof;

R^5 and R^6 are independently H, halogen, CH_3 or CF_3; and

R^7 and R^8 are independently H or halogen;

or a pharmaceutically suitable salt thereof; provided that R^5, R^6 and R^7 cannot all be H and that when R^1 is cyclohexyl and R^3 is H, R^6 must all be Cl or F, but R^6 and R^8 cannot both be Cl.

3. An antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 21.

4. An antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 22.

5. An antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 23.

6. An antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 24.

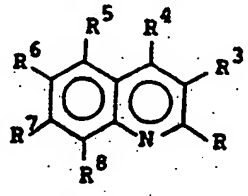
7. An antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 25.

8. An antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 26.

9. An antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 27.

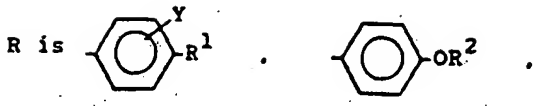
10. An antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 28.

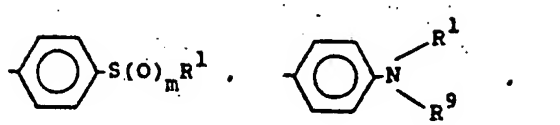
11. Use of at least one compound having the formula:

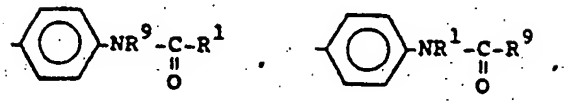


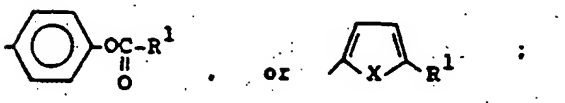
(I)

wherein

R is  ,

 ,

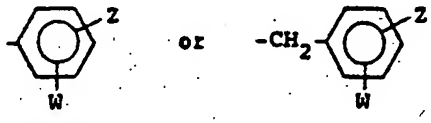
 ,

 ,

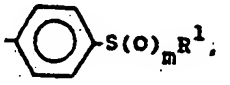
 or ;

X is O, $S(O)_q$, NH or CH=N;

R^1 is $CH_3CH_2(CH_3)CH$, alkyl of 5—12 carbon atoms, alkenyl of 5—12 carbon atoms, cycloalkyl of 3—7 carbon atoms, cycloalkylalkyl of 5—12 carbon atoms, cycloalkenyl of 5—7 carbon atoms.

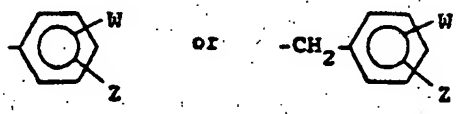
 or .

when R is

 ;

R^1 can be in addition alkyl of 3—4 carbon atoms;

R^2 is

 or ;

R^3 is H, alkoxy of 1—3 carbon atoms, alkylthio of 1—3 carbon atoms or alkyl of 1—3 carbon atoms optionally substituted with one or more of F, Cl, Br or $(CH_2)_pCOR^{10}$ where p is 1, 2, 3 or 4;

R^4 is CO_2H or CO_2R^{11};

R^5, R^6, R^7 and R^8 are independently H, F, Cl, Br, I, CH_3, CF_3, $S(O)_nR^{12}$ or CH_2CH_3, at least two of R^5, R^6, R^7 and R^8 being H;

R^9 and R^{9A} are independently H or alkyl of 1 to 3 carbon atoms;

R^{10} is OH, OCH_3, OCH_2CH_3, NH_2, $NHCH_3$ or $N(CH_3)_2$;

R^{11} is $(CH_2)_{2-4}NR^9R^{9A}$;

R^{12} is alkyl or 1—5 carbon atoms optionally substituted with one or more of F, Cl and Br;

W, Y and Z are independently H, F, Cl, Br, alkyl of 1—5 carbon atoms, NO_2, alkoxy of 1—5 carbon atoms, alkylthio of 1—5 carbon atoms, OH, CF_3 or NH_2;

m is 0 or 1;

n is 0 or 1; and

q is 0, 1 or 2;

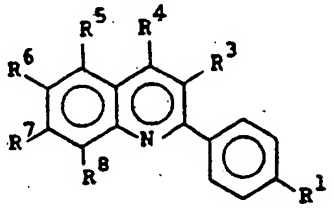
or a pharmaceutically suitable salt thereof; with the following provisos:

1) R^5, R^6 and R^7 cannot all be H;

2) when R^4 is $CO_2CH_2CH_2N(CH_3)_2$, R^6 is CH_2CH_3, or R^7 is Cl, R^1 cannot be cyclohexyl; and

3) when R^1 is cyclohexyl and R^3 is H, R^6 must be Cl or F, but R^5 and R^8 cannot both be Cl in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

12. Use of at least one compound having the formula:



(II)

wherein

R^1 is cycloalkyl or 3—7 carbon atoms; phenyl; phenyl substituted with one halogen, alkyl of 1—5 carbon atoms or CF_3; phenoxy; or phenoxy substituted with one halogen or alkyl of 1—5 carbon atoms;

R^3 is H or alkyl of 1—3 carbon atoms;

R^4 is CO_2H or a sodium or potassium salt thereof;

R^5 and R^6 are independently H, halogen, CH_3 or CF_3; and

R^7 and R^8 are independently H or halogen;

or a pharmaceutically suitable salt thereof; provided that R^5, R^6 and R^7 cannot all be H and that when R^1 is cyclohexyl and R^3 is H, R^6 must be Cl or F, but R^6 and R^8 cannot both be Cl, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

13. Use of at least one compound of Claim 21, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

14. Use of at least one compound of Claim 22, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

15. Use of at least one compound of Claim 23, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

16. Use of at least one compound of Claim 24, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

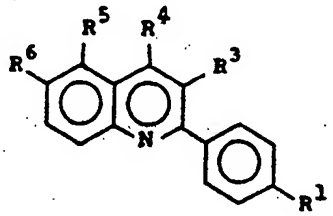
17. Use of at least one compound of Claim 25, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

18. Use of at least one compound of Claim 26, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

19. Use of at least one compound of Claim 27, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

20. Use of at least one compound of Claim 28, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

21. A compound having the formula:



(III)

wherein

R^1 is cycloalkyl of 3—7 carbon atoms,

R^3 is H or alkyl of 1—3 carbon atoms;

R^4 is CO_2H or a sodium or potassium salt thereof;

R^5 and R^6 are independently H, halogen or CF_3 provided that both R^5 and R^6 are not hydrogen; and

W and Z are independently H, halogen, alkyl of 1—5 carbon atoms or CF_3;

provided that when R^1 is phenyl or phenoxy, and R^5 is H, then R^6 cannot be Br; and that when R^1 is cyclohexyl and R^3 is H, R^6 must be Cl or F.

22. A compound of Claim 21 wherein:

R^1 is phenyl, phenyl substituted with at least one halogen, phenoxy, or phenoxy substituted with at least one halogen;

R^3 is methyl;

R^5 is H or Cl; and

R^6 is F or Cl.

23. The compound of Claim 21 which is 2-(1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinolinecarboxylic acid, sodium or potassium salt.

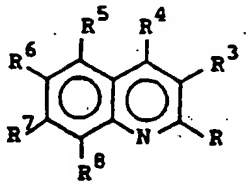
24. The compound of Claim 21 which is 6-fluoro-3-methyl-2-(4-phenoxyphenyl)-4-quinolinecarboxylic acid, sodium or potassium salt.

25. The compound of Claim 21 which is 2-(4'-bromo-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinoline-carboxylic acid, sodium or potassium salt.

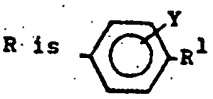
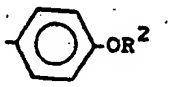
26. The compound of Claim 21 which is 2-(2'-fluoro-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinoline-carboxylic acid, sodium or potassium salt.

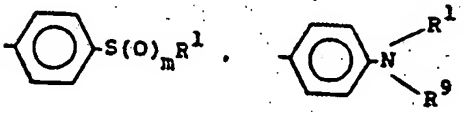
27. The compound of Claim 21 which is 2-(1,1'-biphenyl-4-yl)-5-chloro-6-fluoro-3-methyl-4-quinoline-carboxylic acid, sodium or potassium salt.

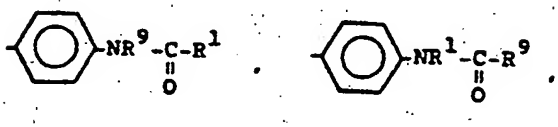
28. A compound having the formula:

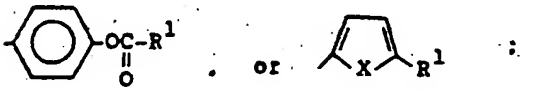


wherein

R is  .  .

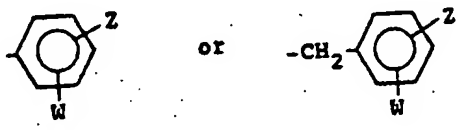




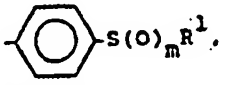


X is O, $S(O)_q$, NH or CH=N;

R^1 is $CH_3CH_2(CH_3)CH$, alkyl of 5—12 carbon atoms, alkenyl of 5—12 carbon atoms, cycloalkyl of 3—7 carbon atoms, cycloalkylalkyl of 5—12 carbon atoms, cycloalkenyl of 5—7 carbon atoms.

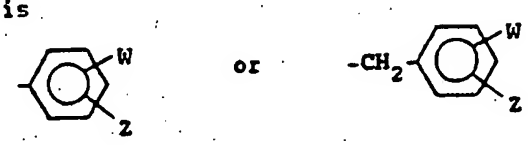


when R is



R^1 can be in addition alkyl of 3—4 carbon atoms;

R^2 is



R^3 is H, alkoxy of 1—3 carbon atoms, alkylthio of 1—3 carbon atoms or alkyl of 1—3 carbon atoms optionally substituted with one or more of F, Cl, Br or $(CH_2)_pCOR^{10}$ where p is 1, 2, 3 or 4;

R^4 is CO_2H or CO_2R^{11};

R^5, R^6, R^7 and R^8 are independently H, F, Cl, Br, I, CH_3, CF_3, $S(O)_nR^{12}$ or CH_2CH_3, at least two of R^5, R^6, R^7 and R^8 being H;

R^9 and R^{9A} are independently H or alkyl of 1 to 3 carbon atoms;

R^{10} is OH, OCH_3, OCH_2CH_3, NH_2, $NHCH_3$ or $N(CH_3)_2$;

R^{11} is $(CH_2)_{2-4}NR^9R^{9A}$;

R^{12} is alkyl or 1—5 carbon atoms optionally substituted with one or more of F, Cl and Br;

W, Y and Z are independently H, F, Cl, Br, alkyl of 1—5 carbon atoms, NO_2, alkoxy of 1—5 carbon atoms, alkylthio of 1—5 carbon atoms, OH, CF_3 or NH_2;

m is 0 or 1;

n is 0 or 1; and

q is 0, 1 or 2;

or a pharmaceutically suitable salt thereof; with the following provisos:

1) when R^4 is CO_2H, R^1 is phenyl or phenoxy, and R^5, R^7 and R^8 are H, R^6 cannot be Br;

2) R^5, R^6 and R^7 cannot all be H;

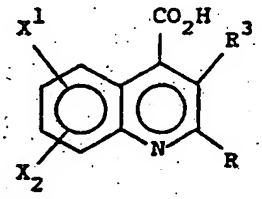
3) when R^4 is $CO_2CH_2CH_2N(CH_3)_2$, R^6 is CH_2CH_3, or R^7 is Cl, R^1 cannot be cyclohexyl;

4) when R^1 is cyclohexyl and R^3 is H, R^6 must be Cl or F, but R^6 and R^8 cannot both be Cl;

5) when R^1 is 4—$H_2NC_6H_4$ and R^3 is H, R^6 cannot be Cl and R^8 cannot be Br;

6) when R^1 is alkyl of 6 carbons and Y is H, then R^4 cannot be CO_2H, R^5, R^7 and R^8 cannot be H, and R^6 cannot be H, Cl, Br, I or CH_3.

29. A process for preparing compounds of Claim 28 characterized by reacting a quinoline carboxylic acid of the formula:



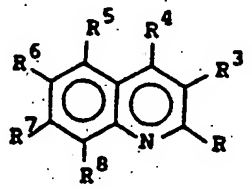
by (a) when R is OH; acylating the hydroxy with a carboxylic halide such as benzoyl chloride in an inert solvent such as chloroform or a hydrocarbon solvent such as benzene at a temperature from 0°C to the boiling point of the solvent, optionally in the presence of a base such as pyridine, or (b) reacting the appropriately substituted quinoline carboxylic acid with an appropriate thiolate $R^{12}S$ such as MeSK in a solvent such as dimethylformamide at a temperature of 50°C to reflux of this solvent, or (c) dissolving the

quinoline carboxylic acid in a protic solvent such as ethanol, and then treating with a metal oxide or hydroxide such as sodium or potassium oxide or hydroxide or an amine such as 1-amino-butanol or lysine at a temperature of 0°C to the boiling point of the solvent used and optionally preparing a salt of an amine group by dissolving the amine in a solvent such as ethyl ether and adding a mineral acid such as HCl; or (d) treating the salt, (c), by treatment with a reagent such as $SOCl_2$ or oxalyl chloride in an inert solvent such as benzene at a temperature of 25°C to the boiling point of the solvent used to form an acid halide and then adding an alcohol, $R^{11}OH$, in a solvent such as tetrahydrofuran at a temperature of 10°C to the boiling point of the solvent used, optionally in the presence of a base such as pyridine, triethylamine, or 4-dimethylamine pyridine.

30. A process for preparing the compounds of Claim 28 consisting essentially of (1) reacting an appropriately substituted isatin (IV) with a substituted ketone (V) in a solvent such as ethanol with a base such as dimethylamine or triethylamine at a temperature of 25°C to 50°C for 2 to 48 hours, (2) dissolving the resulting intermediate (VI) in an appropriate solvent such as tetrahydrofuran containing 25—50% by volume of a mineral acid such as HCl and heating from 50°C to reflux temperature of the solvent mixture for 2 to 48 hours, and optionally the above quinoline carboxylic acid from (2) is further reacted by (a) acylating the corresponding hydroxy, where R is OH, with a carboxylic halide such as benzoyl chloride in an inert solvent such as chloroform or a hydrocarbon solvent such as benzene at a temperature from 0°C to the boiling point of the solvent, optionally in the presence of a base such as pyridine, or (b) reacting the appropriately substituted quinoline carboxylic acid with an appropriate thiolate $R^{12}S$ such as MeSK in a solvent such as dimethylformamide at a temperature of 50°C to reflux of the solvent, or (c) dissolving the quinoline carboxylic acid in a protic solvent such as ethanol, and then treating with a metal oxide or hydroxide such as sodium or potassium oxide or hydroxide or an amine such as 1-amino-butanol or lysine at a temperature of 0°C to the boiling point of the solvent used and optionally preparing a salt of an amine group by dissolving the amine in a solvent such as ethyl ether and adding a mineral acid such as HCl; or (d) treating the salt, (c), by treatment with a reagent such as $SOCl_2$ or oxalyl chloride in an inert solvent such as benzene at a temperature of 25°C to the boiling point of the solvent used to form an acid halide and then adding an alcohol, $R^{11}OH$, in a solvent such as tetrahydrofuran at a temperature of 10°C to the boiling point of the solvent used, optionally in the presence of a base such as pyridine, triethylamine, or 4-dimethylamine pyridine.

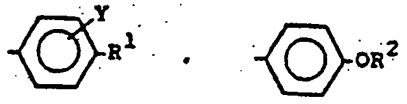
Claims for the Contracting State: AT

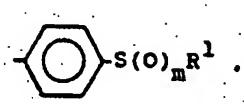
1. Process for preparing an antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound having the formula:

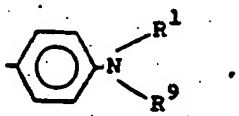


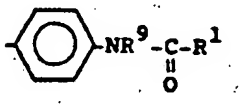
(I)

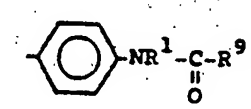
wherein

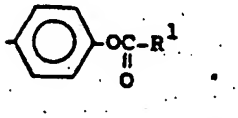
R is  ,

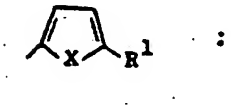
 ,

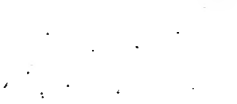
 ,

 ,

 ,

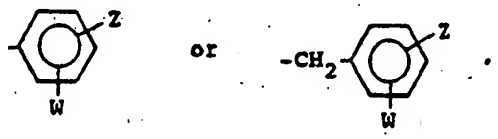
 ,

 ,

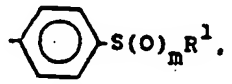
 , or  :

X is O, $S(O)_q$, NH or CH=N;

R^1 is $CH_3CH_2(CH_3)CH$, alkyl of 5—12 carbon atoms, alkenyl of 5—12 carbon atoms, cycloalkyl of 3—7 carbon atoms, cycloalkylalkyl of 5—12 carbon atoms, cycloalkenyl of 5—7 carbon atoms.

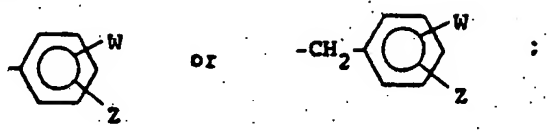


when R is



R^1 can be in addition alkyl of 3—4 carbon atoms;

R^2 is



R^3 is H, alkoxy of 1—3 carbon atoms, alkylthio of 1—3 carbon atoms or alkyl of 1—3 carbon atoms optionally substituted with one or more of F, Cl, Br or $(CH_2)_pCOR^{10}$ where p is 1, 2, 3 or 4;

R^4 is CO_2H or CO_2R^{11};

R^5, R^6, R^7 and R^8 are independently H, F, Cl, Br, I, CH_3, CF_3, $S(O)_nR^{12}$ or CH_2CH_3, at least two of R^5, R^6, R^7 and R^8 being H;

R^9 and R^{9A} are independently H or alkyl of 1 to 3 carbon atoms;

R^{10} is OH, OCH_3, OCH_2CH_3, NH_2, $NHCH_3$ or $N(CH_3)_2$;

R^{11} is $(CH_2)_{2-4}NR^9R^{9A}$;

R^{12} is alkyl or 1—5 carbon atoms optionally substituted with one or more of F, Cl and Br;

W, Y and Z are independently H, F, Cl, Br, alkyl of 1—5 carbon atoms, NO_2, alkoxy of 1—5 carbon atoms, alkylthio of 1—5 carbon atoms, OH, CF_3 or NH_2;

m is 0 or 1;

n is 0 or 1; and

q is 0, 1 or 2;

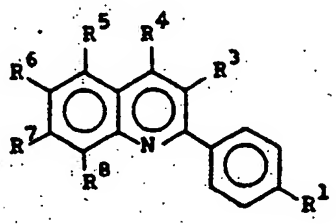
or a pharmaceutically suitable salt thereof; with the following provisos:

1) R^5, R^6 and R^7 cannot all be H;

2) when R^4 is $CO_2CH_2CH_2N(CH_3)_2$, R^8 is CH_2CH_3, or R^7 is Cl, R^1 cannot be cyclohexyl; and

3) when R^1 is cyclohexyl and R^3 is H, R^6 must be Cl or F, but R^6 and R^8 cannot both be Cl, which comprises mixing at least one compound with a suitable pharmaceutical carrier.

2. Process for preparing an antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound having the formula:



(II)

wherein

R^1 is cycloalkyl of 3—7 carbon atoms; phenyl; phenyl substituted with one halogen, alkyl of 1—5 carbon atoms or CF_3; phenoxy; or phenoxy substituted with one halogen or alkyl of 1—5 carbon atoms;

R^3 is H or alkyl of 1—3 carbon atoms;

R^4 is CO_2H or a sodium or potassium salt thereof;

R^5 and R^6 are independently H, halogen, CH_3 or CF_3; and

R^7 and R^8 are independently H or halogen;
or a pharmaceutically suitable salt thereof; provided that R^5, R^6 and R^7 cannot all be H and that when R^1 is cyclohexyl and R^3 is H, R^6 must all be Cl or F, but R^6 and R^8 cannot both be Cl, which comprises mixing at least one compound and a suitable pharmaceutical carrier.

3. Process for preparing an antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 21, which comprises mixing at least one compound and a suitable pharmaceutical carrier.

4. Process for preparing an antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 22, which comprises mixing at least one compound and a suitable pharmaceutical carrier.

5. Process for preparing an antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 23, which comprises mixing at least one compound and a suitable pharmaceutical carrier.

6. Process for preparing an antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 24, which comprises mixing at least one compound and a suitable pharmaceutical carrier.

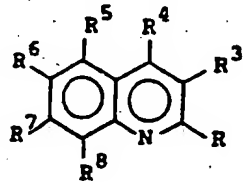
7. Process for preparing an antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 25, which comprises mixing at least one compound and a suitable pharmaceutical carrier.

8. Process for preparing an antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 26, which comprises mixing at least one compound and a suitable pharmaceutical carrier.

9. Process for preparing an antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 27, which comprises mixing at least one compound and a suitable pharmaceutical carrier.

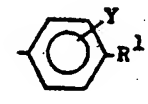
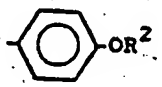
10. Process for preparing an antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 28, which comprises mixing at least one compound and a suitable pharmaceutical carrier.

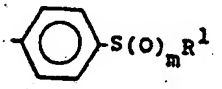
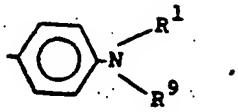
11. Use of at least one compound having the formula:

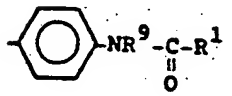
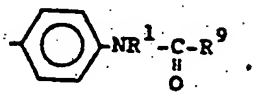


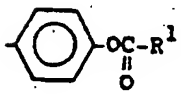
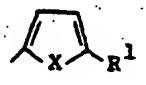
(I)

wherein

R is  .  .

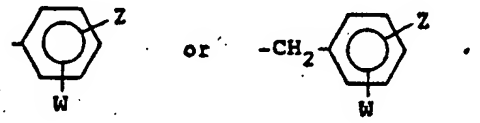
 .  .

 .  .

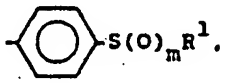
 . or  :

X is O, $S(O)_q$, NH or CH=N;

R^1 is $CH_3CH_2(CH_3)CH$, alkyl of 5—12 carbon atoms, alkenyl of 5—12 carbon atoms, cycloalkyl of 3—7 carbon atoms, cycloalkylalkyl of 5—12 carbon atoms, cycloalkenyl of 5—7 carbon atoms.

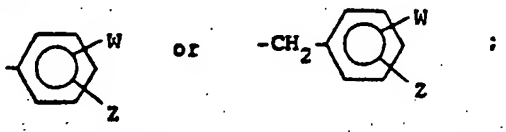


when R is



R^1 can be in addition alkyl of 3—4 carbon atoms;

R^2 is



R^3 is H, alkoxy of 1—3 carbon atoms, alkylthio of 1—3 carbon atoms or alkyl of 1—3 carbon atoms optionally substituted with one or more of F, Cl, Br or $(CH_2)_pCOR^{10}$ where p is 1, 2, 3 or 4;

R^4 is CO_2H or CO_2R^{11};

R^5, R^6, R^7 and R^8 are independently H, F, Cl, Br, I, CH_3, CF_3, $S(O)_nR^{12}$ or CH_2CH_3, at least two of R^5, R^6, R^7 and R^8 being H;

R^9 and R^{9A} are independently H or alkyl of 1 to 3 carbon atoms;

R^{10} is OH, OCH_3, OCH_2CH_3, NH_2, $NHCH_3$ or $N(CH_3)_2$;

R^{11} is $(CH_2)_{2-4}NR^9R^{9A}$;

R^{12} is alkyl or 1—5 carbon atoms optionally substituted with one or more of F, Cl and Br;

W, Y and Z are independently H, F, Cl, Br, alkyl of 1—5 carbon atoms, NO_2, alkoxy of 1—5 carbon atoms, alkylthio of 1—5 carbon atoms, OH, CF_3 or NH_2;

m is 0 or 1;

n is 0 or 1; and

q is 0, 1 or 2;

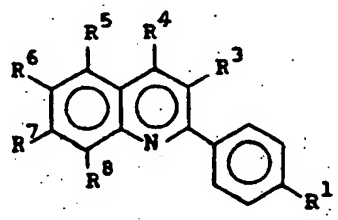
or a pharmaceutically suitable salt thereof; with the following provisos:

1) R^5, R^6 and R^7 cannot all be H;

2) when R^4 is $CO_2CH_2CH_2N(CH_3)_2$, R^6 is CH_2CH_3, or R^7 is Cl, R^1 cannot be cyclohexyl; and

3) when R^1 is cyclohexyl and R^3 is H, R^6 must be Cl or F, but R^6 and R^8 cannot both be Cl in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

12. Use of at least one compound having the formula:



(II)

wherein

R^1 is cycloalkyl or 3—7 carbon atoms; phenyl; phenyl substituted with one halogen, alkyl or 1—5 carbon atoms or CF_3; phenoxy; or phenoxy substituted with one halogen or alkyl of 1—5 carbon atoms;

R^3 is H or alkyl of 1—3 carbon atoms;

R^4 is CO_2H or a sodium or potassium salt thereof;

R^5 and R^6 are independently H, halogen, CH_3 or CF_3; and

R^7 and R^8 are independently H or halogen;

or a pharmaceutically suitable salt thereof; provided that R^5, R^6 and R^7 cannot all be H and that when R^1 is cyclohexyl and R^3 is H, R^6 must be Cl or F, but R^6 and R^8 cannot both be Cl, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

13. Use of at least one compound of Claim 21, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

14. Use of at least one compound of Claim 22, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

15. Use of at least one compound of Claim 23, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

16. Use of at least one compound of Claim 24, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

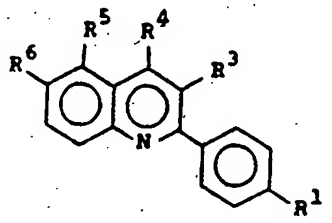
17. Use of at least one compound of Claim 25, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

18. Use of at least one compound of Claim 26, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

19. Use of at least one compound of Claim 27, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

20. Use of at least one compound of Claim 28, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

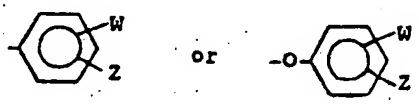
21. A process for preparing a compound having the formula:



(III)

wherein

R^1 is cycloalkyl of 3—7 carbon atoms,



R^3 is H or alkyl of 1—3 carbon atoms;

R^4 is CO_2H or a sodium or potassium salt thereof;

R^5 and R^6 are independently H, halogen or CF_3 provided that both R^5 and R^6 are not hydrogen; and

W and Z are independently H, halogen, alkyl of 1—5 carbon atoms or CF_3;

provided that when R^1 is phenyl or phenoxy, and R^5 is H, then R^6 cannot be Br; and that when R^1 is cyclohexyl and R^3 is H, R^6 must be Cl or F, which comprises (1) reacting an appropriately substituted isatin (IV) with a substituted ketone (V) in a solvent such as ethanol with a base such as diethylamine or triethylamine at a temperature of 25°C to 50°C for 2 to 48 hours, (2) dissolving the resulting intermediate (VI) in an appropriate solvent such as tetrahydrofuran containing 25—50% by volume of a mineral acid such as HCl and heating from 50°C to reflux temperature of the solvent mixture for 2 to 48 hours, and optionally the above quinoline carboxylic acid from (2) is further reacted by (a) acylating the corresponding hydroxy, where R is OH, with a carboxylic halide such as benzoyl chloride in an inert solvent such as chloroform or a hydrocarbon solvent such as benzene at a temperature from 0°C to the boiling point of the solvent, optionally in the presence of a base such as pyridine, or (b) reacting the appropriately substituted quinoline carboxylic acid with an appropriate thiolate $R^{12}S$ such as MeSK in a solvent such as dimethylformamide at a temperature of 50°C to reflux of the solvent, or (c) dissolving the quinoline carboxylic acid in a protic solvent such as ethanol, and then treating with a metal oxide or hydroxide such as sodium or potassium oxide or hydroxide or an amine such as 1-amino-butanol or lysine at a temperature of 0°C to the boiling point of the solvent used and optionally preparing a salt of an amine group by dissolving the amine in a solvent such as ethyl ether and adding a mineral acid such as HCl; or (d) treating the salt, (c), by treatment with a reagent such as $SOCl_2$ or oxalyl chloride in an inert solvent such as benzene at a temperature of 25°C to the boiling point of the solvent used to form an acid halide and then adding an alcohol, $R^{11}OH$, in a solvent such as tetrahydrofuran at a temperature of 10°C to the boiling point of the solvent used, optionally in the presence of a base such as pyridine, triethylamine, or 4-dimethylamine pyridine.

22. A process of Claim 21 wherein:

R^1 is phenyl, phenyl substituted with at least one halogen, phenoxy, or phenoxy substituted with at least one halogen;

R^3 is methyl;

R^5 is H or Cl; and

R^6 is F or Cl.

23. The process of Claim 21 wherein the compound prepared is 2-(1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinolinecarboxylic acid, sodium or potassium salt.

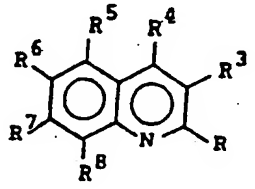
24. The process of Claim 21 wherein the compound prepared is 6-fluoro-3-methyl-2-(4-phenoxyphenyl)-4-quinolinecarboxylic acid, sodium or potassium salt.

25. The process of Claim 21 wherein the compound prepared is 2-(4'-bromo-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinolinecarboxylic acid, sodium or potasslum salt.

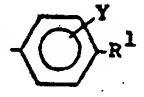
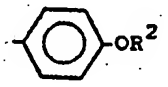
26. The process of Claim 21 wherein the compound prepared is 2-(2'-fluoro-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinolinecarboxylic acid, sodium or potassium salt.

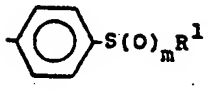
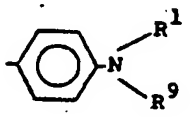
27. The process of Claim 21 wherein the compound prepared is 2-(1,1'-biphenyl-4-yl)-5-chloro-6-fluoro-3-methyl-4-quinolinecarboxylic acid, sodium or potassium salt.

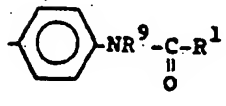
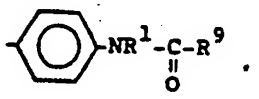
28. Process for preparing a compound having the formula:

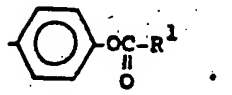
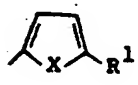


wherein

R is  .  .

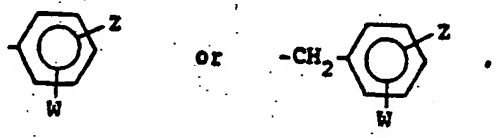
 .  .

 .  .

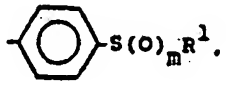
 . or  ;

X is O, $S(O)_q$, NH or CH=N;

R^1 is $CH_3CH_2(CH_3)CH$, alkyl of 5—12 carbon atoms, alkenyl of 5—12 carbon atoms, cycloalkyl of 3—7 carbon atoms, cycloalkylalkyl of 5—12 carbon atoms, cycloalkenyl of 5—7 carbon atoms.

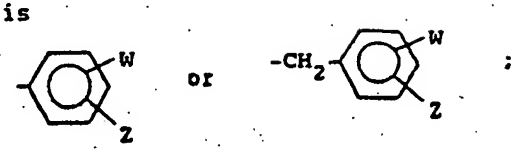


when R is



R^1 can be in addition alkyl of 3—4 carbon atoms;

R^2 is



;

R^3 is H, alkoxy of 1—3 carbon atoms, alkylthio of 1—3 carbon atoms or alkyl of 1—3 carbon atoms optionally substituted with one or more of F, Cl, Br or $(CH_2)_pCOR^{10}$ where p is 1, 2, 3 or 4;

R^4 is CO_2H or CO_2R^{11};

R^5, R^6, R^7 and R^8 are independently H, F, Cl, Br, I, CH_3, CF_3, $S(O)_nR^{12}$ or CH_2CH_3, at least two of R^5, R^6, R^7 and R^8 being H;

R^9 and R^{9A} are independently H or alkyl of 1 to 3 carbon atoms;

R^{10} is OH, OCH_3, OCH_2CH_3, NH_2, $NHCH_3$ or $N(CH_3)_2$;

R^{11} is $(CH_2)_{2-4}NR^9R^{9A}$;

R^{12} is alkyl or 1—5 carbon atoms optionally substituted with one or more of F, Cl and Br;

W, Y and Z are independently H, F, Cl, Br, alkyl of 1—5 carbon atoms, NO_2, alkoxy of 1—5 carbon atoms, alkylthio of 1—5 carbon atoms, OH, CF_3 or NH_2;

m is 0 or 1;

n is 0 or 1; and

q is 0, 1 or 2;

or a pharmaceutically suitable salt thereof; with the following provisos:

1) when R^4 is CO_2H, R^1 is phenyl or phenoxy, and R^5, R^7 and R^8 are H, R^6 cannot be Br;

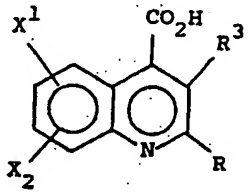
2) R^5, R^6 and R^7 cannot all be H;

3) when R^4 is $CO_2CH_2CH_2N(CH_3)_2$, R^6 is CH_2CH_3, or R^7 is Cl, R^1 cannot be cyclohexyl;

4) when R^1 is cyclohexyl and R^3 is H, R^6 must be Cl or F, but R^6 and R^8 cannot both be Cl;

5) when R^1 is 4—$H_2NC_6H_4$ and R^3 is H, R^6 cannot be Cl and R^8 cannot be Br;

6) when R^1 is alkyl of 6 carbons and Y is H, then R^4 cannot be CO_2H, R^5, R^7 and R^8 cannot be H, and R^6 cannot be H, Cl, Br, I or CH_3, characterized by reacting a quinoline carboxylic acid of the formula:



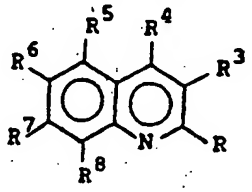
by (a) when R is OH; acylating the hydroxy with a carboxylic halide such as benzoyl chloride in an inert solvent such as chloroform or a hydrocarbon solvent such as benzene at a temperature from 0°C to the boiling point of the solvent, optionally in the presence of a base such as pyridine, or (b) reacting the appropriately substituted quinoline carboxylic acid with an appropriate thiolate $R^{12}S$ such as MeSK in a solvent such as dimethylformamide at a temperature of 50°C to reflux of this solvent, or (c) dissolving the quinoline carboxylic acid in a protic solvent such as ethanol, and then treating with a metal oxide or hydroxide such as sodium or potassium oxide or hydroxide or an amine such as 1-amino-butanol or lysine at a temperature of 0°C to the boiling point of the solvent used and optionally preparing a salt of an amine group by dissolving the amine in a solvent such as ethyl ether and adding a mineral acid such as HCl; or (d) treating the salt, (c), by treatment with a reagent such as $SOCl_2$ or oxalyl chloride in an inert solvent such as benzene at a temperature of 25°C to the boiling point of the solvent used to form an acid halide and then adding an alcohol, $R^{11}OH$, in a solvent such as tetrahydrofuran at a temperature of 10°C to the boiling point of the solvent used, optionally in the presence of a base such as pyridine, triethylamine, or 4-dimethylamine pyridine.

29. A process for preparing the compounds of Claim 28 consisting essentially of (1) reacting an appropriately substituted isatin (IV) with a substituted ketone (V) in a solvent such as ethanol with a base such as dimethylamine or triethylamine at a temperature of 25°C to 50°C for 2 to 48 hours, (2) dissolving the resulting intermediate (VI) in an appropriate solvent such as tetrahydrofuran containing 25—50% by volume of a mineral acid such as HCl and heating from 50°C to reflux temperature of the solvent mixture for 2 to 48 hours, and optionally the above quinoline carboxylic acid from (2) is further reacted by (a) acylating the corresponding hydroxy, where R is OH, with a carboxylic halide such as benzoyl chloride in an inert solvent such as chloroform or a hydrocarbon solvent such as benzene at a temperature from 0°C to the

boiling point of the solvent, optionally in the presence of a base such as pyridine, or (b) reacting the appropriately substituted quinoline carboxylic acid with an appropriate thiolate $R^{12}S$ such as MeSK in a solvent such as dimethylformamide at a temperature of 50°C to reflux of the solvent, or (c) dissolving the quinoline carboxylic acid in a protic solvent such as ethanol, and then treating with a metal oxide or hydroxide such as sodium or potassium oxide or hydroxide or an amine such as 1-amino-butanol or lysine at a temperature of 0°C to the boiling point of the solvent used and optionally preparing a salt of an amine group by dissolving the amine in a solvent such as ethyl ether and adding a mineral acid such as HCl; or (d) treating the salt, (c), by treatment with a reagent such as $SOCl_2$ or oxalyl chloride in an inert solvent such as benzene at a temperature of 25°C to the boiling point of the solvent used to form an acid halide and then adding an alcohol, $R^{11}OH$, in a solvent such as tetrahydrofuran at a temperature of 10°C to the boiling point of the solvent used, optionally in the presence of a base such as pyridine, triethylamine, or 4-dimethylamine pyridine.

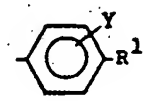
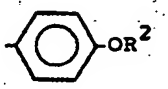
Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

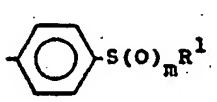
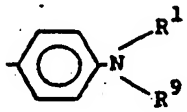
1. Pharmazeutische Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung der Formel

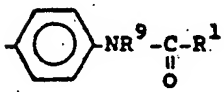
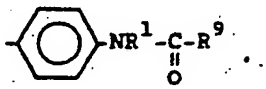


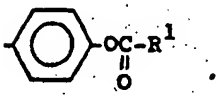
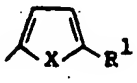
(I)

worin

R  .  .

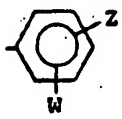
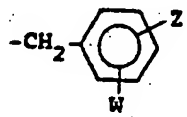
 .  .

 .  .

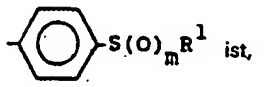
 . oder  ist;

X O, $S(O)_q$, NH oder CH=N ist;

R^1 $CH_3CH_2(CH_3)CH$, Alkyl mit 5—12 Kohlenstoff-Atomen, Alkenyl mit 5—12 Kohlenstoff-Atomen, Cycloalkyl mit 3—7 Kohlenstoff-Atomen, Cycloalkylalkyl mit 5—12 Kohlenstoff-Atomen, Cycloalkenyl mit 5—7 Kohlenstoff-Atomen,

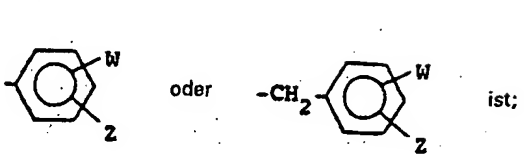
 oder 

ist, wenn



ist,

kann R^1 zusätzlich Alkyl mit 3—4 Kohlenstoff-Atomen sein;



ist;

R^3 H, Alkoxy mit 1—3 Kohlenstoff-Atomen, Alkylthio mit 1—3 Kohlenstoff-Atomen oder Alkyl mit 1—3 Kohlenstoff-Atomen ist, welches gegebenenfalls mit einem oder mehreren F, Cl, Br oder $(CH_2)_pCOR^{10}$, worin p 1, 2, 3 oder 4 ist, substituiert ist;

R^4 CO_2H oder CO_2R^{11} ist;

R^5, R^6, R^7 und R^8 unabhängig voneinander H, F, Cl, Br, I, CH_3, CF_3, $S(O)_nR^{12}$ oder CH_2CH_3 sind, wobei wenigstens zwei von R^5, R^6, R^7 und R^8 H sind;

R^9 und R^{9A} unabhängig voneinander H oder Alkyl mit 1 bis 3 Kohlenstoff-Atomen sind;

R^{10} OH, OCH_3, OCH_2CH_3, NH_2, $NHCH_3$ oder $N(CH_3)_2$ ist;

R^{11} $(CH_2)_{2-4}NR^9R^{9A}$ ist;

R^{12} Alkyl mit 1—5 Kohlenstoffatomen ist, welches gegebenenfalls mit einem oder mehreren F, Cl und Br substituiert ist;

W, Y und Z unabhängig voneinander H, F, Cl, Br, Alkyl mit 1—5 Kohlenstoff-Atomen, NO_2, Alkoxy mit 1—5 Kohlenstoff-Atomen, Alkylthio mit 1—5 Kohlenstoff-Atomen, OH, CF_3 oder NH_2 sind;

m 0 oder 1 ist;

n oder 1 ist; und

q 0, 1 oder 2 ist;

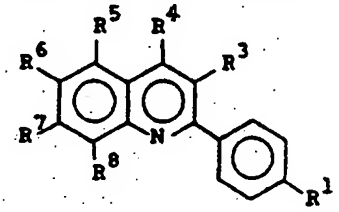
oder einem pharmazeutisch geeigneten Salz derselben; vorausgesetzt, daß:

1) R^5, R^6 und R^7 nicht alle H sein können;

2) wenn R^4 $CO_2CH_2CH_2N(CH_3)_2$ ist, R^6 CH_2CH_3 ist oder R^7 Cl ist, R^1 nicht Cyclohexyl sein kann; und

3) wenn R^1 Cyclohexyl ist und R^3 H ist, R^6 Cl oder F sein muß, aber R^6 und R^8 nicht beide Cl sein können.

2. Pharmazeutische Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung der Formel



(II)

worin

R^1 Cycloalkyl mit 3—7 Kohlenstoff-Atomen, Phenyl, mit einem Halogen, Alkyl mit 1—5 Kohlenstoff-Atomen oder CF_3 substituiertes Phenyl, Phenoxy, oder mit einem Halogen oder Alkyl mit 1—5 Kohlenstoff-Atomen substituiertes Phenoxy ist;

R^3 H oder Alkyl mit 1—3 Kohlenstoff-Atomen ist;

R^4 CO_2H oder dessen Natrium- oder Kaliumsalz ist;

R^5 und R^6 unabhängig voneinander H, Halogen, CH_3 oder CF_3 sind; und

R^7 und R^8 unabhängig voneinander H oder Halogen sind; oder ein pharmazeutisch geeignetes Salz derselben;

vorausgesetzt, daß R^5, R^6 und R^7 nicht alle H sein können und daß, wenn R^1 Cyclohexyl ist und R^3 H ist, R^6 Cl oder F sein muß, aber R^6 und R^8 nicht beide Cl sein können.

3. Pharmazeutische Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 21.

4. Pharmazeutische Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 22.

5. Pharmazeutische Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 23.

6. Pharmazeutische Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 24.

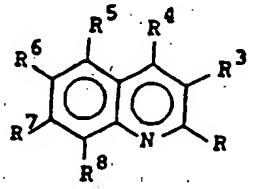
7. Pharmazeutische Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 25.

8. Pharmazeutische Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 26.

9. Pharmazeutische Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 27.

10. Pharmazeutische Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 28.

11. Verwendung wenigstens einer Verbindung der Formel



(I)

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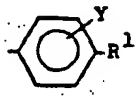
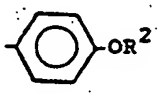
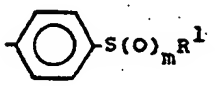
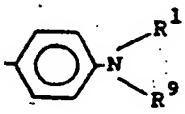
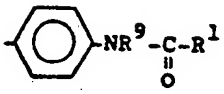
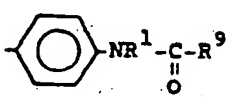
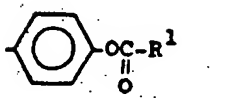
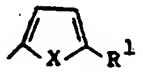
R  .  .

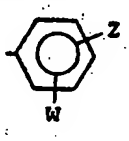
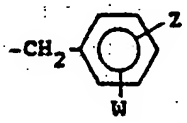
 .  .

 .  .

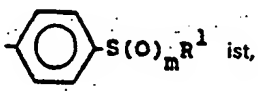
 oder  ist;

X O, $S(O)_q$, NH oder CH=N ist;

R^1 $CH_3CH_2(CH_3)CH$, Alkyl mit 5—12 Kohlenstoff-Atomen, Alkenyl 5—12 Kohlenstoff-Atomen, Alkenyl mit 5—12 Kohlenstoff-Atomen, Cycloalkyl mit 3—7 Kohlenstoff-Atomen, Cycloalkylalkyl mit 5—12 Kohlenstoff-Atomen, Cycloalkenyl mit 5—7 Kohlenstoff-Atomen,

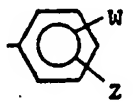
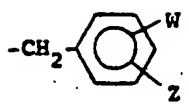
 oder  ist,

wenn

R  ist,

kann R^1 zusätzlich Alkyl mit 3—4 Kohlenstoff-Atomen sein;

R^2


oder

ist;

R^3 H, Alkoxy mit 1—3 Kohlenstoff-Atomen, Alkylthio mit 1—3 Kohlenstoff-Atomen oder Alkyl mit 1—3 Kohlenstoff-Atomen ist, welches gegebenenfalls mit einem oder mehreren F, Cl, Br oder $(CH_2)_pCOR^{10}$, worin p 1, 2, 3 oder 4 ist, substituiert ist;

R^4 CO_2H oder CO_2R^{11} ist;

R^5, R^6, R^7 und R^8 unabhängig voneinander H, F, Cl, Br, I, CH_3, CF_3, $S(O)_nR^{12}$ oder CH_2CH_3 sind, wobei wenigstens zwei von R^5, R^6, R^7 und R^8 H sind;

R^9 und R^{9A} unabhängig voneinander H oder Alkyl mit 1 bis 3 Kohlenstoff-Atomen sind;

R^{10} OH, OCH_3, OCH_2CH_3, NH_2, $NHCH_3$ oder $N(CH_3)_2$ ist;

R^{11} $(CH_2)_{2-4}NR^9R^{9A}$ ist;

R^{12} Alkyl mit 1—5 Kohlenstoffatomen ist, welches gegebenenfalls mit einem oder mehreren F, Cl und Br substituiert ist;

W, Y und Z unabhängig voneinander H, F, Cl, Br, Alkyl mit 1—5 Kohlenstoff-Atomen, NO_2, Alkoxy mit 1—5 Kohlenstoff-Atomen, Alkylthio mit 1—5 Kohlenstoff-Atomen, OH, CF_3 oder NH_2 sind;

m 0 oder 1 ist;

n 0 oder 1 ist; und

q 0, 1 oder 2 ist;

oder einem pharmazeutisch geeigneten Salz derselben; vorausgesetzt, daß:

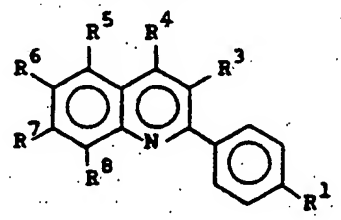
1) R^5, R^6 und R^7 nicht alle H sein können;

2) wenn R^4 $CO_2CH_2CH_2N(CH_3)_2$ ist, R^6 CH_2CH_3 ist oder R^7 Cl ist, R^1 nicht Cyclohexyl sein kann; und

3) wenn R^1 Cyclohexyl ist und R^3 H ist, R^6 Cl oder F sein muß, aber R^6 und R^8 nicht beide Cl sein können,

in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.

12. Verwendung wenigstens einer Verbindung der Formel


(II)

worin

R^1 Cycloalkyl mit 3—7 Kohlenstoff-Atomen, Phenyl, mit einem Halogen, Alkyl mit 1—5 Kohlenstoff-Atomen oder CF_3 substituiertes Phenyl, Phenoxy, oder mit einem Halogen oder Alkyl mit 1—5 Kohlenstoff-Atomen substituiertes Phenoxy ist;

R^3 H oder Alkyl mit 1—3 Kohlenstoff-Atomen ist;

R^4 CO_2H oder dessen Natrium- oder Kaliumsalz ist;

R^5 und R^6 unabhängig voneinander H, Halogen, CH_3 oder CF_3 sind; und

R^7 und R^8 unabhängig voneinander H oder Halogen sind; oder ein pharmazeutisch geeignetes Salz derselben; vorausgesetzt, daß R^5, R^6 und R^7 nicht alle H sein können und daß, wenn R^1 Cyclohexyl ist und R^3 H ist, R^6 Cl oder F sein muß, aber R^6 und R^8 nicht beide Cl sein können, in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.

13. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 21 in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.

14. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 22 in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.

15. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 23 in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.

16. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 24 in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.

17. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 25 in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.

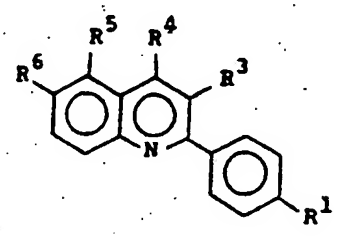
18. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 26 in einer tumor-

inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.

19. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 27 in einer tumorinhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.

20. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 28 in einer tumorinhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.

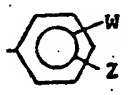
21. Verbindung der Formel



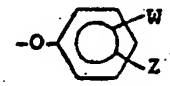
(III)

worin

R^1 Cycloalkyl mit 3—7 Kohlenstoff-Atomen,



oder



ist;

R^3 H oder Alkyl mit 1—3 Kohlenstoff-Atomen ist;

R^4 CO_2H oder dessen Natrim- oder Kaliumsalz ist;

R^5 und R^6 unabhängig voneinander H, Halogen oder CF_3 sind, vorausgesetzt, daß R^5 und R^6 nicht beide Wasserstoff sind; und W und Z unabhängig voneinander H, Halogen, Alkyl mit 1—5 Kohlenstoff-Atomen oder CF_3 sind;

vorausgesetzt, daß, wenn R^1 Phenyl oder Phenoxy ist und R^5 H ist, R^6 nicht Br sein kann, und daß, wenn R^1 Cyclohexyl und R^3 H ist, R^6 Cl oder F sein muß.

22. Verbindung des Anspruchs 21, worin

R^1 Phenyl, mit wenigstens einem Halogen substituiertes Phenyl, Phenoxy oder mit wenigstens einem Halogen substituiertes Phenoxy ist;

R^3 Methyl ist;

R^5 H oder Cl ist; und

R^6 F oder Cl ist.

23. Verbindung des Anspruchs 21, welche 2-(1,1'-Biphenyl-4-yl)-6-fluor-3-methyl-4-chinolincarbonsäure, -Natrium- oder -Kalium-Salz ist.

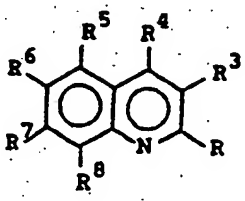
24. Verbindung des Anspruchs 21, welche 6-Fluor-3-methyl-2-(4-phenoxyphenyl)-4-chinolincarbonsäure, -Natrium- oder -Kalium-Salz ist.

25. Verbindung des Anspruchs 21, welche 2-(4'-Brom-1,1'-biphenyl-4-yl)-6-fluor-3-methyl-4-chinolincarbonsäure, -Natrium- oder -Kalium-Salz ist.

26. Verbindung des Anspruchs 21, welche 2-(2'-Fluor-1,1'-biphenyl-4-yl)-6-fluor-3-methyl-4-chinolincarbonsäure, -Natrium- oder -Kalium-Salz ist.

27. Verbindung des Anspruchs 21, welche 2-(1,1'-Biphenyl-4-yl)-5-chlor-6-fluor-3-methyl-4-chinolincarbonsäure, -Natrium- oder -Kalium-Salz ist.

28. Verbindung der Formel



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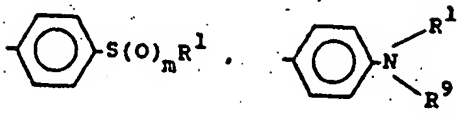
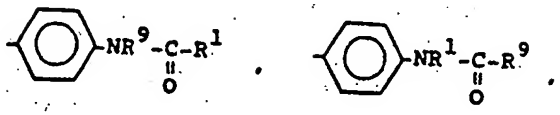
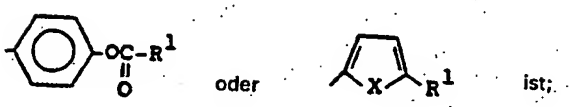
R  ,

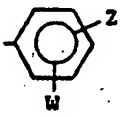
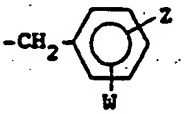
 ,

 ,

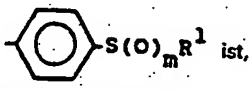
 oder ist;

X O, $S(O)_q$, NH oder CH=N ist;

R^1 $CH_3CH_2(CH_3)CH$, Alkyl mit 5—12 Kohlenstoff-Atomen, Alkenyl mit 5—12 Kohlenstoff-Atomen, Cycloalkyl mit 3—7 Kohlenstoff-Atomen, Cycloalkylalkyl mit 5—12 Kohlenstoff-Atomen, Cycloalkenyl mit 5—7 Kohlenstoff-Atomen,

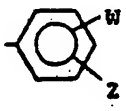
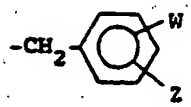
 oder  ist,

wenn

R  ist,

kann R^1 zusätzlich Alkyl mit 3—4 Kohlenstoff-Atomen sein;

R^2

 oder  ist;

R^3 H, Alkoxy mit 1—3 Kohlenstoff-Atomen, Alkylthio mit 1—3 Kohlenstoff-Atomen oder Alkyl mit 1—3 Kohlenstoff-Atomen ist, welches gegebenenfalls mit einem oder mehreren F, Cl, Br oder $(CH_2)_pCOR^{10}$, worin p 1, 2, 3 oder 4 ist, substituiert ist;

R^4 CO_2H oder CO_2R^{11} ist;

R^5, R^6, R^7 und R^8 unabhängig voneinander H, F, Cl, Br, I, CH_3, CF_3, $S(O)_nR^{12}$ oder CH_2CH_3 sind, wobei wenigstens zwei von R^5, R^6, R^7 und R^8 H sind;

R^9 und R^{9A} unabhängig voneinander H oder Alkyl mit 1 bis 3 Kohlenstoff-Atomen sind;

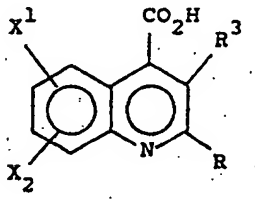
R^{10} OH, OCH_3, OCH_2CH_3, NH_2, $NHCH_3$ oder $N(CH_3)_2$ ist;

R^{11} $(CH_2)_{2-4}NR^9R^{9A}$ ist;

R^{12} Alkyl mit 1—5 Kohlenstoffatomen ist, welches gegebenenfalls mit einem oder mehreren F, Cl und Br substituiert ist;

W, Y und Z unabhängig voneinander H, F, Cl, Br, Alkyl mit 1—5 Kohlenstoff-Atomen, NO_2, Alkoxy mit 1—5 Kohlenstoff-Atomen, Alkylthio mit 1—5 Kohlenstoff-Atomen, OH, CF_3 oder NH_2 sind;
m 0 oder 1 ist;
n oder 1 ist; und
q 0, 1 oder 2 ist;
oder einem pharmazeutisch geeigneten Salz derselben; vorausgesetzt, daß:
1) wenn R^4 CO_2H ist, R^1 Phenyl oder Phenoxy ist und R^5, R^7 und R^8 H sind, R^6 nicht Br sein kann;
2) R^5, R^6 und R^7 nicht alle H sein können;
3) wenn R^4 $CO_2CH_2CH_2N(CH_3)_2$ ist, R^6 CH_2CH_3 ist oder R^7 Cl ist, R^1 nicht Cyclohexyl sein kann;
4) wenn R^1 Cyclohexyl ist und R^3 H ist, R^6 Cl oder F sein muß, aber R^6 und R^8 nicht beide Cl sein können;
5) wenn R^1 4-$H_2NC_6H_4$ und R^3 H ist, R^6 nicht Cl sein kann und R^8 nicht Br sein kann;
6) wenn R^1 Alkyl mit 6 Kohlenstoffatomen ist und Y H ist, R^4 nicht CO_2H sein kann, R^5, R^7 und R^8 nicht H sein können und R^6 nicht H, Cl, Br, I oder CH_3 sein kann.

29. Verfahren zur Herstellung von Verbindungen des Anspruchs 28 gekennzeichnet durch Umsetzung einer Chinolincarbonsäure der Formel

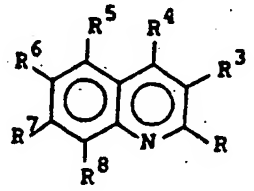


durch (a), wenn R OH ist, Acylierung der Hydroxygruppe mit einem Carboxylhalogenid wie Benzoylchlorid in einem inerten Lösungsmittel wie Chloroform oder einem Kohlenwasserstoff-Lösungsmittel wie Benzol bei einer Temperatur von 0°C bis zum Siedepunkt des Lösungsmittels, wahlweise in Gegenwart einer Base wie Pyridin, oder (b) Umsetzung der geeignet substituierten Chinolincarbonsäure mit einem geeigneten Thiolat $R^{12}S$ wie MeSK in einem Lösungsmittel wie Dimethylformamide bei einer Temperatur von 50°C bis zum Rückfluß des Lösungsmittels, oder (c) Lösen der Chinolincarbonsäure in einem protischen Lösungsmittel wie Ethanol und dann Behandeln mit einem Metalloxid oder -hydroxid wie Natrium- oder Kalium-oxid oder -hydroxid oder einem Amin wie 1-Aminobutanol oder Lysin bei einer Temperatur von 0°C bis zum Seidepunkt des verwendeten Lösungsmittels und wahlweise Herstellung eines Salzes einer Aminogruppe durch Lösen des Amins in einem Lösungsmittel wie Ethylether und Zugabe einer Mineralsäure wie HCl; oder (d) Behandeln des Salzes (c), durch Behandlung mit einem Reagenz wie $SOCl_2$ oder Oxalylchlorid in einem inerten Lösungsmittel wie Benzol bei einer Temperatur von 25°C bis zum Siedepunkt des verwendeten Lösungsmittels unter Bildung eines Säurehalogenids und dann zugabe eines Alkohols, $R^{11}OH$, in einem Lösungsmittel wie Tetrahydrofuran bei einer Temperatur von 10°C bis zum Siedepunkt des verwendeten Lösungsmittels, wahlweise in Gegenwart einer Base wie Pyridin, Triethylamin oder 4-Dimethylminopyridin.

30. Verfahren zur Herstellung der Verbindungen von Anspruch 28, im wesentlichen bestehend aus (1) Umsetzung eines geeignet substituierten Isatins (IV) mit einem substituierten Keton (V) in einem Lösungsmittel wie Ethanol mit einer Base wie Diethylamin oder Triethylamin bei einer Temperatur von 25°C bis 50°C für 2 bis 48 Stunden, (2) Lösen der entstandenen Zwischenstufe (VI) in einem geeigneten Lösungsmittel wie Tetrahydrofuran, welches 25—50 Vol.-% einer Mineralsäure wie HCl enthält, und 2 bis 48 Stunden Erhitzen auf 50°C bis zur Rückflußtemperatur des Lösungsmittelgemischs, und wahlweise wird die voranstehende Chinolincarbonsäure aus (2) weiter umgesetzt durch (a) Acylierung der entsprechenden Hydroxygruppe, in der R OH ist, mit einem Carboxylhalogenid wie Benzoylchlorid in einem inerten Lösungsmittel wie Chloroform oder einem Kohlenwasserstoff-Lösungsmittel wie Benzol bei einer Temperatur von 0°C bis zum Siedepunkt des Lösungsmittel, wahlweise in der Gegenwart einer Base wie Pyridin, oder (b) durch Umsetzung der geeignet substituierten Chinolincarbonsäure mit einem geeigneten Thiolat $R^{12}S$ wie MeSK in einem Lösungsmittel wie Dimethylformamid bei einer Temperatur von 50°C bis zum Rückfluß des Lösungsmittels oder (c) durch Lösen der Chinolincarbonsäure in einem protischen Lösungsmittel wie Ethanol, und dann Behandeln mit einem Metalloxid oder -hydroxid wie Natrium- oder Kaliumoxid oder -hydroxid oder einem Amin wie 1-Aminobutanol oder Lysin bei einer Temperatur von 0°C bis zum Siedepunkt des verwendeten Lösungsmittels und wahlweise Herstellen eines Salzes einer Aminogruppe durch Lösen des Amins in einem Lösungsmittel wie Ethylether und Zugabe einer Mineralsäure wie HCl, oder (d) Behandeln des Salzes, (c) durch Behandlung mit einem Reagenz wie $SOCl_2$ oder Oxalylchlorid in einem inerten Lösungsmittel wie Benzol bei einer Temperatur von 25°C bis zum Siedepunkt des verwendeten Lösungsmittels unter Bildung eines Säurehalogenids und dann Zugabe eines Alkohols, $R^{11}OH$, in einem Lösungsmittel wie Tetrahydrofuran bei einer Temperatur von 10°C bis zum Siedepunkt des verwendeten Lösungsmittels, wahlweise in Gegenwart einer Base wie Pyridin, Triethylamine oder 4-Dimethylaminopyridin.

Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung einer pharmazeutischen Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung der Formel



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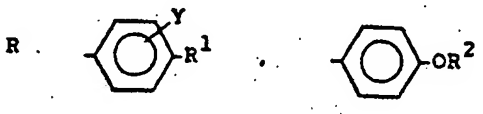
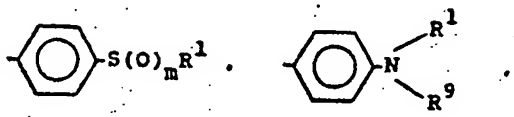
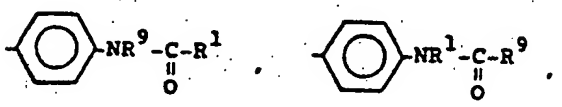
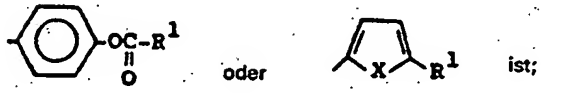




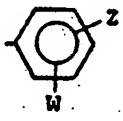
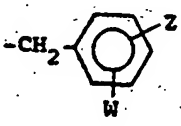




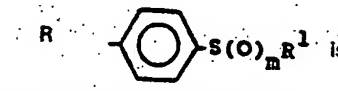
 oder ist;

X O, $S(O)_o$, NH oder CH=N ist;

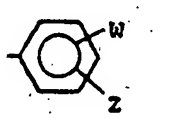
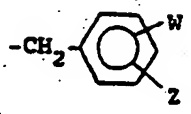
R^1 $CH_3CH_2(CH_3)CH$, Alkyl mit 5—12 Kohlenstoff-Atomen, Alkenyl mit 5—12 Kohlenstoff-Atomen, Cycloalkyl mit 3—7 Kohlenstoff-Atomen, Cycloalkylalkyl mit 5—12 Kohlenstoff-Atomen, Cycloalkenyl mit 5—7 Kohlenstoff-Atomen,

 oder  ist,

wenn

 ist,

kann R^1 zusätzlich Alkyl mit 3—4 Kohlenstoff-Atomen sein;

 oder  ist;

R^3 H, Alkoxy mit 1—3 Kohlenstoff-Atomen, Alkylthio mit 1—3 Kohlenstoff-Atomen oder Alkyl mit 1—3 Kohlenstoff-Atomen ist, welches gegebenenfalls mit einem oder mehreren F, Cl, Br oder $(CH_2)_pCOR^{10}$, worin p 1, 2, 3 oder 4 ist, substituiert ist;

R^4 CO_2H oder CO_2R^{11} ist;

R^5, R^6, R^7 und R^8 unabhängig voneinander H, F, Cl, Br, I, CH_3, CF_3, $S(O)_nR^{12}$ oder CH_2CH_3 sind, wobei wenigstens zwei von R^5, R^6, R^7 und R^8 H sind;

R^9 und R^{9A} unabhängig voneinander H oder Alkyl mit 1 bis 3 Kohlenstoff-Atomen sind;

R^{10} OH, OCH_3, OCH_2CH_3, NH_2, $NHCH_3$ oder $N(CH_3)_2$ ist;

R^{11} $(CH_2)_{2-4}NR^9R^{9A}$ ist;

R^{12} Alkyl mit 1—5 Kohlenstoffatomen ist, welches gegebenenfalls mit einem oder mehreren F, Cl und Br substituiert ist;

W, Y und Z unabhängig voneinander H, F, Cl, Br, Alkyl mit 1—5 Kohlenstoff-Atomen, NO_2, Alkoxy mit 1—5 Kohlenstoff-Atomen, Alkylthio mit 1—5 Kohlenstoff-Atomen, OH, CF_3 oder NH_2 sind;

m 0 oder 1 ist;

n oder 1 ist; und

q 0, 1 oder 2 ist;

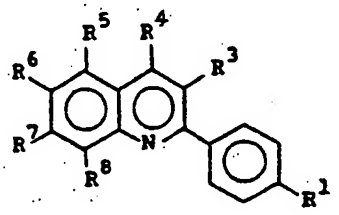
oder einem pharmazeutisch geeigneten Salz derselben; vorausgesetzt, daß:

1) R^5, R^6 und R^7 nicht alle H sein können;

2) wenn R^4 $CO_2CH_2CH_2N(CH_3)_2$ ist, R^6 CH_2CH_3 ist oder R^7 Cl ist, R^1 nicht Cyclohexyl sein kann; und

3) wenn R^1 Cyclohexyl ist und R^3 H ist, R^6 Cl oder F sein muß, aber R^8 und R^8 nicht beide Cl sein können, umfassend das Vermischen mindestens einer Verbindung mit einem geeigneten Träger.

2. Verfahren zur Herstellung einer pharmazeutischen Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung der Formel



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R^1 Cycloalkyl mit 3—7 Kohlenstoff-Atomen, Phenyl, mit einem Halogen, Alkyl mit 1—5 Kohlenstoff-Atomen oder CF_3 substituiertes Phenyl, Phenoxy, oder mit einem Halogen oder Alkyl mit 1—5 Kohlenstoff-Atomen substituiertes Phenoxy ist;

R^3 H oder Alkyl mit 1—3 Kohlenstoff-Atomen ist;

R^4 CO_2H oder dessen Natrium- oder Kaliumsalz ist;

R^5 und R^6 unabhängig voneinander H, Halogen, CH_3 oder CF_3 sind; und

R^7 und R^8 unabhängig voneinander H oder Halogen sind; oder ein pharmazeutisch geeignetes Salz derselben;

vorausgesetzt, daß R^5, R^6 und R^7 nicht alle H sein können und daß, wenn R^1 Cyclohexyl ist und R^3 H ist, R^6 Cl oder F sein muß, aber R^8 und R^8 nicht beide Cl sein können, umfassend das Vermischen mindestens einer Verbindung mit einem geeigneten Träger.

3. Verfahren zur Herstellung einer pharmazeutischen Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 21, umfassend das Vermischen mindestens einer Verbindung mit einem geeigneten Träger.

4. Verfahren zur Herstellung einer pharmazeutischen Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 22, umfassend das Vermischen mindestens einer Verbindung mit einem geeigneten Träger.

5. Verfahren zur Herstellung einer pharmazeutischen Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 23, umfassend das Vermischen mindestens einer Verbindung mit einem geeigneten Träger.

6. Verfahren zur Herstellung einer pharmazeutischen Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 24, umfassend das Vermischen mindestens einer Verbindung mit einem geeigneten Träger.

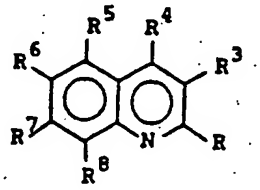
7. Verfahren zur Herstellung einer pharmazeutischen Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 25, umfassend das Vermischen mindestens einer Verbindung mit einem geeigneten Träger.

8. Verfahren zur Herstellung einer pharmazeutischen Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 26, umfassend das Vermischen mindestens einer Verbindung mit einem geeigneten Träger.

9. Verfahren zur Herstellung einer pharmazeutischen Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 27, umfassend das Vermischen mindestens einer Verbindung mit einem geeigneten Träger.

10. Verfahren zur Herstellung einer pharmazeutischen Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 28, umfassend das Vermischen mindestens einer Verbindung mit einem geeigneten Träger.

11. Verwendung wenigstens einer Verbindung der Formel



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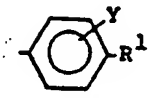
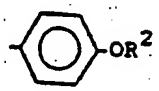
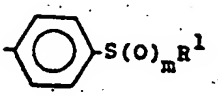
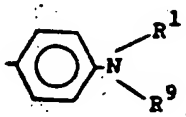
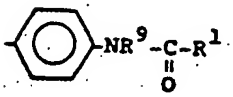
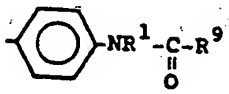
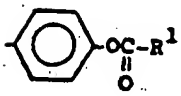
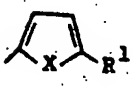
R  .  .

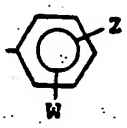
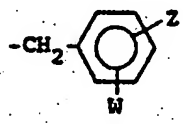
 .  .

 .  .

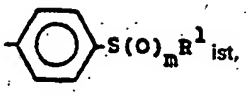
 oder  ist;

X O, $S(O)_q$, NH oder CH=N ist;

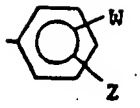
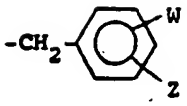
R^1 $CH_3CH_2(CH_3)CH$, Alkyl mit 5—12 Kohlenstoff-Atomen, Alkenyl mit 5—12 Kohlenstoff-Atomen, Cycloalkyl mit 3—7 Kohlenstoff-Atomen, Cycloalkylalkyl mit 5—12 Kohlenstoff-Atomen, Cycloalkenyl mit 5—7 Kohlenstoff-Atomen,

 oder  ist,

wenn

R  ist,

kann R^1 zusätzlich Alkyl mit 3—4 Kohlenstoff-Atomen sein;

R^2  oder  ist;

R^3 H, Alkoxy mit 1—3 Kohlenstoff-Atomen, Alkylthio mit 1—3 Kohlenstoff-Atomen oder Alkyl mit 1—3 Kohlenstoff-Atomen ist, welches gegebenenfalls mit einem oder mehreren F, Cl, Br oder $(CH_2)_pCOR^{10}$, worin p 1, 2, 3 oder 4 ist, substituiert ist;

R^4 CO_2H oder CO_2R^{11} ist;

R^5, R^6, R^7 und R^8 unabhängig voneinander H, F, Cl, Br, I, CH_3, CF_3, $S(O)_nR^{12}$ oder CH_2CH_3 sind, wobei wenigstens zwei von R^5, R^6, R^7 und R^8 H sind;

R^9 und R^{9A} unabhängig voneinander H oder Alkyl mit 1 bis 3 Kohlenstoff-Atomen sind;

R^{10} OH, OCH_3, OCH_2CH_3, NH_2, $NHCH_3$ oder $N(CH_3)_2$ ist;

R^{11} $(CH_2)_{2-4}NR^9R^{9A}$ ist;

R^{12} Alkyl mit 1—5 Kohlenstoffatomen ist, welches gegebenenfalls mit einem oder mehreren F, Cl und Br substituiert ist;

W, Y und Z unabhängig voneinander H, F, Cl, Br, Alkyl mit 1—5 Kohlenstoff-Atomen, NO_2, Alkoxy mit 1—5 Kohlenstoff-Atomen, Alkylthio mit 1—5 Kohlenstoff-Atomen, OH, CF_3 oder NH_2 sind;

m 0 oder 1 ist;

n oder 1 ist; und

q 0, 1 oder 2 ist;

oder einem pharmazeutisch geeigneten Salz derselben; vorausgesetzt, daß:

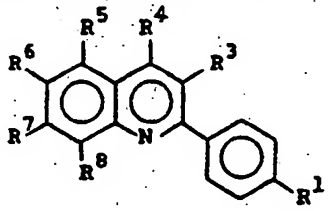
1) R^5, R^6 und R^7 nicht alle H sein können;

2) wenn R^4 $CO_2CH_2CH_2N(CH_3)_2$ ist, R^6 CH_2CH_3 ist oder R^7 Cl ist, R^1 nicht Cyclohexyl sein kann; und

3) wenn R^1 Cyclohexyl ist und R^3 H ist, R^6 Cl oder F sein muß, aber R^6 und R^8 nicht beide Cl sein können,

in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.

12. Verwendung wenigstens einer Verbindung der Formel

 (II)

worin

R^1 Cycloalkyl mit 3—7 Kohlenstoff-Atomen, Phenyl, mit einem Halogen, Alkyl mit 1—5 Kohlenstoff-Atomen oder CF_3 substituiertes Phenyl, Phenoxy, oder mit einem Halogen oder Alkyl mit 1—5 Kohlenstoff-Atomen substituiertes Phenoxy ist;

R^3 H oder Alkyl mit 1—3 Kohlenstoff-Atomen ist;

R^4 CO_2H oder dessen Natrium- oder Kaliumsalz ist;

R^5 und R^6 unabhängig voneinander H, Halogen, CH_3 oder CF_3 sind; und

R^7 und R^8 unabhängig voneinander H oder Halogen sind; oder ein pharmazeutisch geeignetes Salz derselben; vorausgesetzt, daß R^5, R^6 und R^7 nicht alle H sein können und daß, wenn R^1 Cyclohexyl ist und R^3 H ist, R^6 Cl oder F sein muß, aber R^6 und R^8 nicht beide Cl sein können, in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.

13. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 21 in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.

14. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 22 in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.

15. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 23 in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.

16. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 24 in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.

17. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 25 in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.

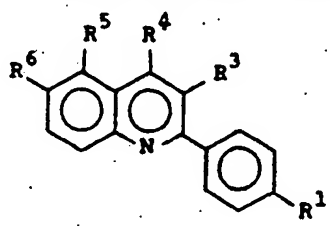
18. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 26 in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.

19. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 27 in einer tumor-

inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.

20. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 28 in einer tumorinhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.

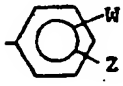
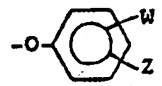
21. Verbindung zur Herstellung einer Verbindung der Formel



(III)

worin

R^1 Cycloalkyl mit 3—7 Kohlenstoff-Atomen,

 oder  ist;

R^3 H oder Alkyl mit 1—3 Kohlenstoff-Atomen ist;

R^4 CO_2H oder dessen Natrim- oder Kaliumsalz ist;

R^5 und R^6 unabhängig voneinander H, Halogen oder CF_3 sind, vorausgesetzt, daß R^5 und R^6 nicht beide Wasserstoff sind; und W und Z unabhängig voneinander H, Halogen, Alkyl mit 1—5 Kohlenstoff-Atomen oder CF_3 sind;

vorausgesetzt, daß, wenn R^1 Phenyl oder Phenoxy ist und R^5 H ist, R^6 nicht Br sein kann, und daß, wenn R^1 Cyclohexyl und R^3 H ist, R^6 Cl oder F sein muß, umfassend

(1) Umsetzung eines geeignet substituierten Isatins (IV) mit einem substituierten Keton (V) in einem Lösungsmittel wie Ethanol mit einer Base wie Diethylamin oder Triethylamin bei einer Temperatur von 25°C bis 50°C für 2 bis 48 Stunden, (2) Lösen der entstandenen Zwischenstufe (VI) in einem geeigneten Lösungsmittel wie Tetrahydrofuran, welches 25—50 Vol.-% einer Mineralsäure wie HCl enthält, und 2 bis 48 Stunden Erhitzen auf 50°C bis zur Rückflußtemperatur des Lösungsmittelgemischs, und wahlweise wird die voranstehende Chinolincarbonsäure aus (2) weiter umgesetzt durch (a) Acylierung der entsprechenden Hydroxygruppe, in der R OH ist, mit einem Carboxylhalogenid wie Benzoylchlorid in einem inerten Lösungsmittel wie Chloroform oder einem Kohlenwasserstoff-Lösungsmittel wie Benzol bei einer Temperatur von 0°C bis zum Siedepunkt des Lösungsmittel, wahlweise in der Gegenwart einer Base wie Pyridin, oder (b) durch Umsetzung der geeignet substituierten Chinolincarbonsäure mit einem geeigneten Thiolat $R^{12}S$ wie MeSK in einem Lösungsmittel wie Dimethylformamid bei einer Temperatur von 50°C bis zum Rückfluß des Lösungsmittels oder (c) durch Lösen der Chinolincarbonsäure in einem protischen Lösungsmittel wie Ethanol, und dann Behandeln mit einem Metalloxid oder -hydroxid wie Natrium- oder Kaliumoxid oder -hydroxid oder einem Amin wie 1-Aminobutanol oder Lysin bei einer Temperatur von 0°C bis zum Siedepunkt des verwendeten Lösungsmittels und wahlweise Herstellen eines Salzes einer Ainogruppe durch Lösen des Amins in einem Lösungsmittel wie Ethylether und Zugabe einer Mineralsäure wie HCl, oder (d) Behandeln des Salzes, (c) durch Behandlung mit einem Reagenz wie $SOCl_2$ oder Oxalylchlorid in einem inerten Lösungsmittel wie Benzol bei einer Temperatur von 25°C bis zum Siedepunkt des verwendeten Lösungsmittels unter Bildung eines Säurehalogenids und dann Zugabe eines Alkohols, $R^{11}OH$, in einem Lösungsmittel wie Tetrahydrofuran bei einer Temperatur von 10°C bis zum Siedepunkt des verwendeten Lösungsmittels, wahlweise in Gegenwart einer Base wie Pyridin, Triethylamine oder 4-Dimethylaminopyridin.

22. Verfahren des Anspruchs 21, worin

R^1 Phenyl, mit wenigstens einem Halogen substituiertes Phenyl, Phenoxy oder mit wenigstens einem Halogen substituiertes Phenoxy ist;

R^3 Methyl ist;

R^5 H oder Cl ist; und

R^6 F oder Cl ist.

23. Verfahren des Anspruchs 21, worin die hergestellte Verbindung 2-(1,1'-Biphenyl-4-yl)-6-fluor-3-methyl-4-chinolincarbonsäure, -Natrium- oder -Kalium-Salz ist.

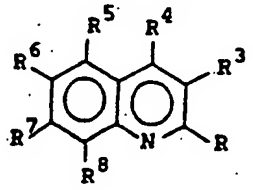
24. Verfahren des Anspruchs 21, worin die hergestellte Verbindung 6-Fluor-3-methyl-2-(4-phenoxyphenyl)-4-chinolincarbonsäure, -Natrium- oder -Kalium-Salz ist.

25. Verfahren des Anspruchs 21, worin die hergestellte Verbindung 2-(4'-Brom-1,1'-biphenyl-4-yl)-6-fluor-3-methyl-4-chinolincarbonsäure, -Natrium- oder -Kalium-Salz ist.

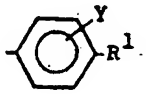
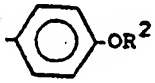
26. Verfahren des Anspruchs 21, worin die hergestellte Verbindung 2-(2'-Fluor-1,1'-biphenyl-4-yl)-6-fluor-3-methyl-4-chinolincarbonsäure, -Natrium- oder -Kalium-Salz ist.

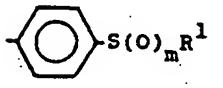
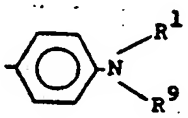
27. Verfahren des Anspruchs 21, worin die hergestellte Verbindung 2-(1,1'-Biphenyl-4-yl)-5-chlor-6-fluor-3-methyl-4-chinolincarbonsäure, -Natrium- oder -Kalium-Salz ist.

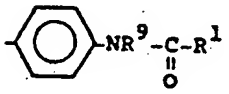
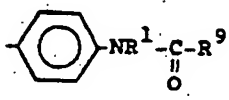
28. Verfahren zur Herstellung einer Verbindung der Formel

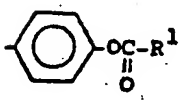
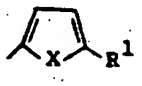


worin

R  ,  ,

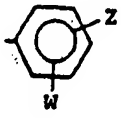
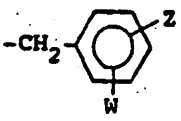
 ,  ,

 ,  ,

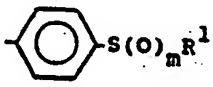
 oder  ist;

X O, $S(O)_a$, NH oder CH=N ist;

R^1 $CH_3CH_2(CH_3)CH$, Alkyl mit 5—12 Kohlenstoff-Atomen, Alkenyl mit 5—12 Kohlenstoff-Atomen, Cycloalkyl mit 3—7 Kohlenstoff-Atomen, Cycloalkylalkyl mit 5—12 Kohlenstoff-Atomen, Cycloalkenyl mit 5—7 Kohlenstoff-Atomen,

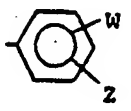
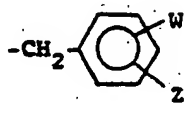
 oder  ist,

wenn

R  ist;

kann R^1 zusätzlich Alkyl mit 3—4 Kohlenstoff-Atomen sein;

R^2

 oder  ist,

R^3 H, Alkoxy mit 1—3 Kohlenstoff-Atomen, Alkylthio mit 1—3 Kohlenstoff-Atomen oder Alkyl mit 1—3 Kohlenstoff-Atomen ist, welches gegebenenfalls mit einem oder mehreren F, Cl, Br oder $(CH_2)_pCOR^{10}$, worin p 1, 2, 3 oder 4 ist, substituiert ist;

R^4 CO_2H oder CO_2R^{11} ist;

R^5, R^6, R^7 und R^8 unabhängig voneinander H, F, Cl, Br, I, CH_3, CF_3, $S(O)_nR^{12}$ oder CH_2CH_3 sind, wobei wenigstens zwei von R^5, R^6, R^7 und R^8 H sind;

R^9 und R^{9A} unabhängig voneinander H oder Alkyl mit 1 bis 3 Kohlenstoff-Atomen sind;

R^{10} OH, OCH_3, OCH_2CH_3, NH_2, $NHCH_3$ oder $N(CH_3)_2$ ist;

R^{11} $(CH_2)_{2-4}NR^9R^{9A}$ ist;

R^{12} Alkyl mit 1—5 Kohlenstoffatomen ist, welches gegebenenfalls mit einem oder mehreren F, Cl und Br substituiert ist;

W, Y und Z unabhängig voneinander H, F, Cl, Br, Alkyl mit 1—5 Kohlenstoff-Atomen, NO_2, Alkoxy mit 1—5 Kohlenstoff-Atomen, Alkylthio mit 1—5 Kohlenstoff-Atomen, OH, CF_3 oder NH_2 sind;

m 0 oder 1 ist;

n oder 1 ist; und

q 0, 1 oder 2 ist;

oder einem pharmazeutisch geeigneten Salz derselben; vorausgesetzt, daß:

1) wenn R^4 CO_2H ist, R^1 Phenyl oder Phenoxy ist und R^5, R^7 und R^8 H sind, R^6 nicht Br sein kann;

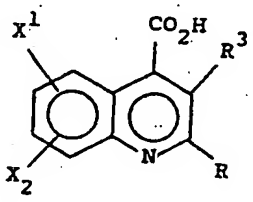
2) R^5, R^6 und R^7 nicht alle H sein können;

3) wenn R^4 $CO_2CH_2CH_2N(CH_3)_2$ ist, R^6 CH_2CH_3 ist oder R^7 Cl ist, R^1 nicht Cyclohexyl sein kann;

4) wenn R^1 Cyclohexyl ist und R^3 H ist, R^6 Cl oder F sein muß, aber R^6 und R^8 nicht beide Cl sein können;

5) wenn R^1 4-$H_2NC_6H_4$ und R^3 H ist, R^6 nicht Cl sein kann und R^8 nicht Br sein kann;

6) wenn R^1 Alkyl mit 6 Kohlenstoffatomen ist und Y H ist, R^4 nicht C O_2H sein kann, R^5, R^7 und R^8 nicht H sein können und R^6 nicht H, Cl, Br, I oder CH_3 sein kann gekennzeichnet durch Umsetzung einer Chinolincarbonsäure der Formel



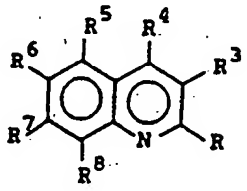
durch (a), wenn R OH ist, Acylierung der Hydroxygruppe mit einem Carboxylhalogenid wie Benzoylchlorid in einem inerten Lösungsmittel wie Chloroform oder einem Kohlenwasserstoff-Lösungsmittel wie Benzol bei einer Temperatur von 0°C bis zum Siedepunkt des Lösungsmittels, wahlweise in Gegenwart einer Base wie pyridin, oder (b) Umsetzung der geeignet substituierten Chinolincarbonsäure mit einem geeigneten Thiolat $R^{12}S$ wie MeSK in einem Lösungsmittel wie Dimethylformamid bei einer Temperatur von 50°C bis zum Rückfluß des Lösungsmittels, oder (c) Lösen der Chinolincarbonsäure in einem protischen Lösungsmittel wie Ethanol und dann Behandeln mit einem Metalloxid oder -hydroxid wie Natrium- oder Kaliumoxid oder -hydroxid oder einem Amin wie 1-Aminobutanol oder Lysin bei einer Temperatur von 0°C bis zum Seidepunkt des verwendeten Lösungsmittels und wahlweise Herstellung eines Salzes einer Aminogruppe durch Lösen des Amins in einem Lösungsmittel wie Ethylether und Zugabe einer Mineralsäure wie HCl, oder (d) Behandeln des Salzes (c), durch Behandlung mit einem Reagenz wie $SOCl_2$ oder Oxalylchlorid in einem inerten Lösungsmittel wie Benzol bei einer Temperatur von 25°C bis zum Siedepunkt des verwendeten Lösungsmittels unter Bildung eines Säurehalogenids und dann zugabe eines Alkohols, $R^{11}OH$, in einem Lösungsmittel wie Tetrahydrofuran bei einer Temperatur von 10°C bis zum Siedepunkt des verwendeten Lösungsmittels, wahlweise in Gegenwart einer Base wie Pyridin, Triethylamin oder 4-Dimethylminopyridin.

29. Verfahren zur Herstellung der Verbindungen des Anspruch 28, im wesentlichen bestehend aus (1) Umsetzung eines geeignet substituierten Isatins (IV) mit einem substituierten Keton (V) in einem Lösungsmittel wie Ethanol mit einer Base wie Diethylamin oder Triethylamin bei einer Temperatur von 25°C bis 50°C für 2 bis 48 Stunden, (2) Lösen der entstandenen Zwischenstufe (VI) in einem geeigneten Lösungsmittel wie Tetrahydrofuran, welches 25—50 Vol.-% einer Mineralsäure wie HCl enthält, und 2 bis 48 Stunden Erhitzen auf 50°C bis zur Rückflußtemperatur des Lösungsmittelgemischs, und wahlweise wird die voranstehende Chinolincarbonsäure (2) weiter umgesetzt durch (a) Acylierung der entsprechenden Hydroxygruppe, in der R OH ist, mit einem Carboxylhalogenid wie Benzoylchlorid in einem inerten Lösungsmittel wie Chloroform oder einem Kohlenwasserstoff-Lösungsmittel wie Benzol bei einer Temperatur von 0°C bis zum Siedepunkt des Lösungsmittels, wahlweise in der Gegenwart einer Base wie pyridin, oder (b) durch Umsetzung der geeignet substituierten Chinolincarbonsäure mit einem geeigneten Thiolat $R^{12}S$ wie MeSK in einem Lösungsmittel wie Dimethylformamid bei einer Temperatur von 50°C bis zum Rückfluß des Lösungsmittels oder (c) durch Lösen der Chinolincarbonsäure in einem protischen

Lösungsmittel wie Ethanol, und dann Behandeln mit einem Metalloxid oder -hydroxid wie Natrium- oder Kaliumoxid oder -hydroxid oder einem Amin wie 1-Aminobutanol oder Lysin bei einer Temperatur von 0°C bis zum Siedepunkt des verwendeten Lösungsmittels und wahlweise Herstellen eines Salzes einer Aminogruppe durch Lösen des Amins in einem Lösungsmittel wie Ethylether und Zugabe einer Mineralsäure wie HCl, oder (d) Behandeln des Salzes, (c) durch Behandlung mit einem Reagenz wie $SOCl_2$ oder Oxalylchlorid in einem inerten Lösungsmittel wie Benzol bei einer Temperatur von 25°C bis zum Siedepunkt des verwendeten Lösungsmittels unter Bildung eines Säurehalogenids und dann Zugabe eines Alkohols, $R^{11}OH$, in einem Lösungsmittel wie Tetrahydrofuran bei einer Temperatur von 10°C bis zum Siedepunkt des verwendeten Lösungsmittels, wahlweise in Gegenwart einer Base wie Pyridin, Triethylamin oder 4-Dimethylaminopyridin.

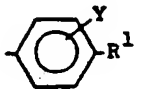
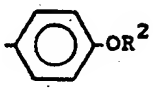
Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

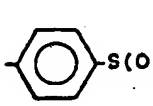
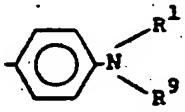
1. Une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé répondant à la formule:

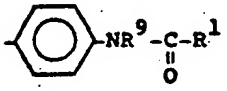
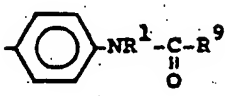


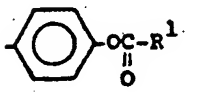
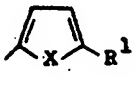
(I)

dans laquelle

R est  .  .

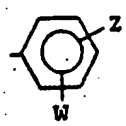
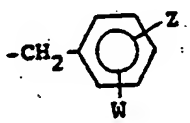
 .  .

 .  .

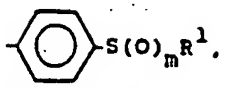
 . ou  :

X est O, $S(O)_q$, NH ou CH=N;

R^1 est un groupe $CH_3CH_2(CH_3)CH$, alkyle de 5 à 12 atomes de carbone, alcényle de 5 à 12 atomes de carbone, cycloalkyle de 3 à 7 atomes de carbone, cycloalkylalkyle de 5 à 12 atomes de carbone, cycloalcényle de 5 à 7 atomes de carbone,

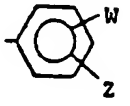
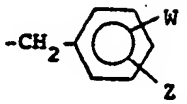
 ou 

lorsque

R est  .

R^1 peut être, de plus, un groupe alkyle de 3 ou 4 atomes de carbone;

R^2 est

 ou  ;

R^3 est H, un groupe alcoxy de 1 à 3 atomes de carbone, alkylthio de 1 à 3 atomes de carbone ou alkyle de 1 à 3 atomes de carbone facultativement substitué par un ou plusieurs de F, Cl, Br ou $(CH_2)_pCOR^{10}$ où p est 1, 2, 3 ou 4;

R^4 est CO_2H ou CO_2R^{11};

R^5, R^6, R^7 et R^8 sont indépendamment H, F, Cl, Br, I, CH_3, CF_3, $S(O)_nR^{12}$ ou CH_2CH_3, au moins deux de R^5, R^6, R^7 et R^8 étant H;

R^9 et R^{9A} sont indépendamment H ou un groupe alkyle de 1 à 3 atomes de carbone;

R^{10} est OH, OCH_3, OCH_2CH_3, NH_2, $NHCH_3$ ou $N(CH_3)_2$;

R^{11} est $(CH_2)_{2-4}NR^9R^{9A}$;

R^{12} est un groupe alkyle de 1 à 5 atomes de carbone facultativement substitué par un ou plusieurs de F, Cl et Br;

W, Y et Z sont indépendamment H, F, Cl, Br, un groupe alkyle de 1 à 5 atomes de carbone, NO_2, alcoxy de 1 à 5 atomes de carbone, alkylthio de 1 à 5 atomes de carbone, OH, CF_3 ou NH_2;

m est 0 ou 1;

n est 0 ou 1; et

q est 0, 1 ou 2;

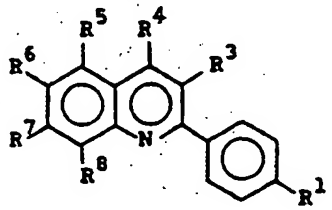
ou un sel pharmaceutiquement acceptable de ce composé; avec les conditions suivantes:

1) R^5, R^6 et R^7 ne peuvent pas tous être H;

2) si R^4 est $CO_2CH_2CH_2N(CH_3)_2$, R^6 est CH_2CH_3 our R^7 est Cl, R^1 ne peut pas être un groupe cyclohexyle; et

3) si R^1 est un groupe cyclohexyle et R^3 est H, R^6 doit être Cl ou F, mais R^6 et R^8 ne peuvent pas être tous deux Cl.

2. Une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé répondant à la formule:

 (II)

dans laquelle

R^1 est un groupe cycloalkyle de 3 à 7 atomes de carbone; phényle; phényle substitué par un halogène, un groupe alkyle de 1 à 5 atomes de carbone ou CF_3; phénoxy; ou phénoxy substitué par un halogène ou un groupe alkyle 1 à 5 atomes de carbone;

R^3 est H ou un groupe alkyle de 1 à 3 atomes de carbone;

R^4 est CO_2H ou son sel de sodium ou de potassium;

R^5 et R^6 sont indépendamment H, un halogène, CH_3 ou CF_3; et

R^7 et R^8 sont indépendamment H ou un halogène

ou un sel pharmaceutiquement acceptable de ce composé; avec la condition que R^5, R^6 et R^7 ne peuvent pas tous être H et que si R^1 est un groupe cyclohexyle et R^3 est H, R^6 doit être Cl ou F, mais R^6 et R^8 peuvent pas être tous deux Cl.

3. Une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 21.

4. Une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 22.

5. Une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 23.

6. Une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 24.

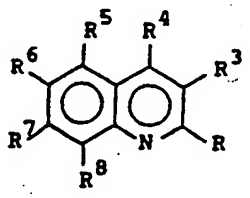
7. Une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 25.

8. Une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 26.

9. Une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 27.

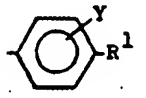
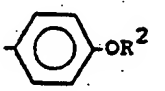
10. Une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 28.

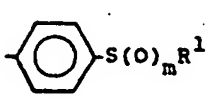
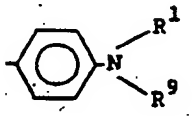
11. Utilisation d'au moins un composé répondant à la formule:

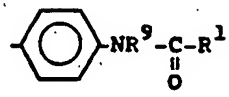
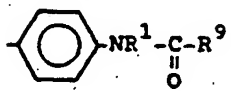


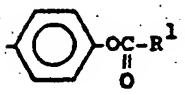
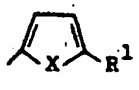
(I)

dans laquelle

R est  .  .

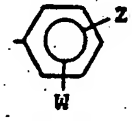
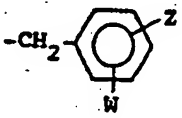
 .  .

 .  .

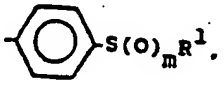
 . ou  :

X est O, $S(O)_q$, NH ou CH=N;

R^1 est un groupe $CH_3CH_2(CH_3)CH$, alkyle de 5 à 12 atomes de carbone, alcényle de 5 à 12 atomes de carbone, cycloalkyle de 3 à 7 atomes de carbone, cycloalkylalkyle de 5 à 12 atomes de carbone, cycloalcényle de 5 à 7 atomes de carbone,

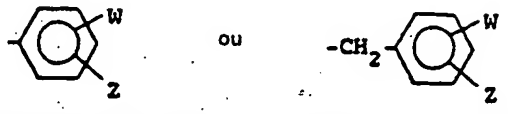
 ou  .

lorsque

R est  .

R^1 peut être, de plus, un groupe alkyle de 3 ou 4 atomes de carbone;

R^2 est



;

R^3 est H, une groupe alcoxy de 1 à 3 atomes de carbone, alkylthio de 1 à 3 atomes de carbone ou alkyle de 1 à 3 atomes de carbone facultativement substitué par un ou plusieurs de F, Cl, Br ou $(CH_2)_pCOR^{10}$ où p est 1, 2, 3 ou 4;

R^4 est CO_2H ou CO_2R^{11};

R^5, R^6, R^7 et R^8 sont indépendamment H, F, Cl, Br, I, CH_3, CF_3, $S(O)_nR^{12}$ ou CH_2CH_3, au moins deux de R^5, R^6, R^7 et R^8 étant H;

R^9 et R^{9A} sont indépendamment H ou un groupe alkyle de 1 à 3 atomes de carbone;

R^{10} est OH, OCH_3, OCH_2CH_3, NH_2, $NHCH_3$ ou $N(CH_3)_2$;

R^{11} est $(CH_2)_{2-4}NR^9R^{9A}$;

R^{12} est un groupe alkyle de 1 à 5 atomes de carbone facultativement substitué par un ou plusieurs de F, Cl et Br;

W, Y et Z sont indépendamment H, F, Cl, Br, un groupe alkyle de 1 à 5 atomes de carbone, NO_2, alcoxy de 1 à 5 atomes de carbone, alkylthio de 1 à 5 atomes de carbone, OH, CF_3 ou NH_2;

m est 0 ou 1;

n est 0 ou 1; et

q est 0, 1 ou 2;

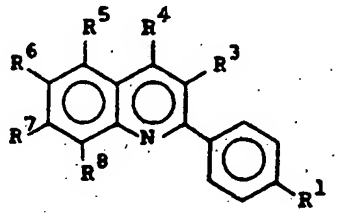
ou un sel pharmaceutiquement acceptable de ce composé; avec les conditions suivantes:

1) R^5, R^6 et R^7 ne peuvent pas tous être H;

2) si R^4 est $CO_2CH_2CH_2N(CH_3)_2$, R^6 est CH_2CH_3 ou R^7 est Cl, R^1 ne peut pas être un groupe cyclohexyle; et

3) si R^1 est un groupe cyclohexyle et R^3 est H, R^6 doit être Cl ou F, mais R^6 et R^8 ne peuvent pas être tous deux Cl, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

12. Utilisation d'au moins un composé répondant à la formule:



(II)

dans laquelle

R^1 est un groupe cycloalkyle de 3 à 7 atomes de carbone; phényle; phényle substitué par un halogène, un groupe alkyle de 1 à 5 atomes de carbone ou CF_3; phénoxy; ou phénoxy substitué par un halogène ou un groupe alkyle 1 à 5 atomes de carbone;

R^3 est H ou un groupe alkyle de 1 à 3 atomes de carbone;

R^4 est CO_2H ou son sel de sodium ou de potassium;

R^5 et R^6 sont indépendamment H, un halogène, CH_3 ou CF_3; et

R^7 et R^8 sont indépendamment H ou un halogène

ou un sel pharmaceutiquement acceptable de ce composé; avec la condition que R^5, R^6 et R^7 ne peuvent pas tous être H et que si R^1 est un groupe cyclohexyle et R^3 est H, R^6 doit être Cl ou F, mais R^6 et R^8 peuvent pas être tous deux Cl, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

13. Utilisation d'au moins un composé de la revendication 21, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

14. Utilisation d'au moins un composé de la revendication 22, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

15. Utilisation d'au moins un composé de la revendication 23, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

16. Utilisation d'au moins un composé de la revendication 24, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

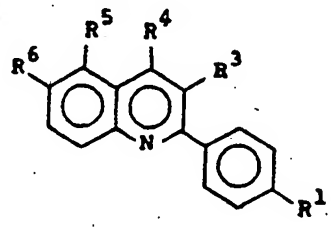
17. Utilisation d'au moins un composé de la revendication 25, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

18. Utilisation d'au moins un composé de la revendication 26, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

19. Utilisation d'au moins un composé de la revendication 27, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

20. Utilisation d'au moins un composé de la revendication 28, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

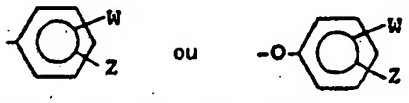
21. Un composé répondant à la formule:



(III)

dans laquelle

R^1 est un groupe cycloalkyle de 3 à 7 atomes de carbone,



;

R^3 est H ou un groupe alkyle de 1 à 3 atomes de carbone;

R^4 est CO_2H ou son sel de sodium ou de potassium;

R^5 et R^6 sont indépendamment H, un halogène ou CF_3, avec la condition que R^5 et R^6 ne soient pas tous deux de l'hydrogène; et

W et Z sont indépendamment H, un halogène, un groupe alkyle de 1 à 5 atomes de carbone ou CF_3; avec la condition que si R^1 est un groupe phényle ou phénoxy et R^5 est H, alors R^6 ne peut pas être Br; et que si R^1 est un groupe cyclohexyle et R^3 est H, R^6 doit être Cl ou F.

22. Un composé de la revendication 21, dans lequel:

R^1 est un groupe phényle, phényle substitué par au moins un halogène ou groupe phénoxy, ou phénoxy substitué par au moins un halogène;

R^3 est un groupe méthyle;

R^5 est H ou Cl; et

R^6 est F ou Cl.

23. Le composé de la revendication 21, qui est le sel de sodium ou de potassium de l'acide 2 - (1,1' - diphényl - 4 - yl) - 6 - fluoro - 3 - méthyl - 4 - quinoléine-carboxylique.

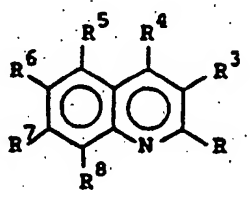
24. Le composé de la revendication 21, qui est le sel de sodium ou de potassium de l'acide 6 - fluoro - 3 - méthyl - 2 - (4 - phénoxyphényl) - 4 - quinoléine-carboxylique.

25. Le composé de la revendication 21, qui est le sel de sodium ou de potassium de l'acide 2 - (4' - bromo - 1,1' - diphényl - 4 - yl) - 6 - fluoro - 3 - méthyl - 4 - quinoléine-carboxylique.

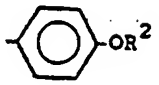
26. Le composé de la revendication 21, qui est le sel de sodium ou de potassium de l'acide 2 - (2' - fluoro - 1,1' - diphényl - 4 - yl) - 6 - fluoro - 3 - méthyl - 4 - quinoléine-carboxylique.

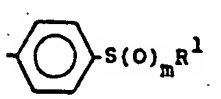
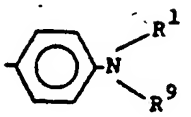
27. Le composé de la revendication 21, qui est le sel de sodium ou de potassium de l'acide 2 - (1,1' - diphényl - 4 - yl) - 5 - chloro - 6 - fluoro - 3 - méthyl - 4 - quinoléine-carboxylique.

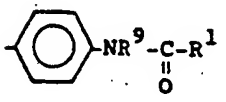
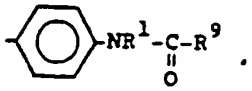
28. Un composé répondant à la formule:

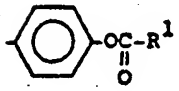
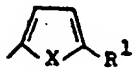


dans laquelle

R est  .  .

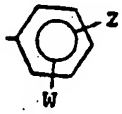
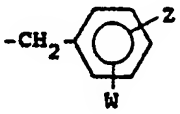
 .  .

 .  .

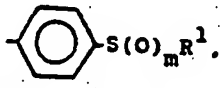
 . ou  ;

X est O, $S(O)_q$, NH ou CH=N;

R^1 est un groupe $CH_3CH_2(CH_3)CH$, alkyle de 5 à 12 atomes de carbone, alcényle de 5 à 12 atomes de carbone, cycloalkyle de 3 à 7 atomes de carbone, cycloalkylalkyle de 5 à 12 atomes de carbone, cycloalcényle de 5 à 7 atomes de carbone,

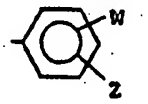
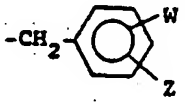
 ou  .

lorsque

R est  .

R^1 peut être, de plus, un groupe alkyle de 3 ou 4 atomes de carbone;

R^2 est

 ou  ;

R^3 est H, une groupe alcoxy de 1 à 3 atomes de carbone, alkylthio de 1 à 3 atomes de carbone ou alkyle de 1 à 3 atomes de carbone facultativement substitué par un ou plusieurs de F, Cl, Br ou $(CH_2)_pCOR^{10}$ où p est 1, 2, 3 ou 4;

R^4 est CO_2H ou CO_2R^{11};

R^5, R^6, R^7 et R^8 sont indépendamment H, F, Cl, Br, I, CH_3, CF_3, $S(O)_nR^{12}$ ou CH_2CH_3, au moins deux de R^5, R^6, R^7 et R^8 étant H;

R^9 et R^{9A} sont indépendamment H ou un groupe alkyle de 1 à 3 atomes de carbone;

R^{10} est OH, OCH_3, OCH_2CH_3, NH_2, $NHCH_3$ ou $N(CH_3)_2$;

R^{11} est $(CH_2)_{2-4}NR^9R^{9A}$;

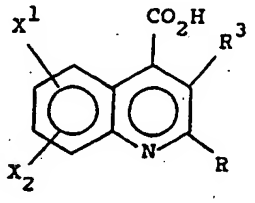
R^{12} est un groupe alkyle de 1 à 5 atomes de carbone facultativement substitué par un ou plusieurs de F, Cl et Br;

W, Y et Z sont indépendamment H, F, Cl, Br, un groupe alkyle de 1 à 5 atomes de carbone, NO_2, alcoxy de 1 à 5 atomes de carbone, alkylthio de 1 à 5 atomes de carbone, OH, CF_3 ou NH_2;

m est 0 ou 1;

n est 0 ou 1; et
q est 0, 1 ou 2;
ou un sel pharmaceutiquement acceptable de ce composé; avec les conditions suivantes:
1) si R^4 est CO_2H, R^1 est un groupe phényle ou phénoxy et R^6, R^7 et R^8 sont H, R^6 ne peut pas être Br;
2) R^5, R^6 et R^7 ne peuvent pas tous être H;
3) si R^4 est $CO_2CH_2CH_2N(CH_3)_2$, R^6 est CH_2CH_3 our R^7 est Cl, R^1 ne peut pas être un groupe cyclohexyle;
4) si R^1 est un groupe cyclohexyle et R^3 est H, R^6 doit être Cl ou F, mais R^6 et R^8 ne peuvent pas être tous deux Cl;
5) si R^1 est 4-$H_2NC_6H_4$ et R^3 est H, R^6 ne peut pas être Cl et R^8 ne peut pas être Br;
6) si R^1 est un groupe alkyle de 6 atomes de carbone et Y est H, alors R^4 ne peut pas être CO_2H, R^5, R^7 et R^8 ne peuvent pas être H, et R^5 neu peut pas être H, Cl, Br, I ou CH_3.

29. Un procédé pour préparer des composés de la revendication 28, caractérisé en ce qu'on fait réagir un acide quinoléine-carboxylique de la formule:

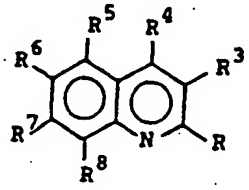


(a) lorsque R est OH, en acylant le groupe hydroxyle avec un halogénure carboxylique tel que le chlorure de benzoyle dans un solvant inerte tel que le chloroforme ou un solvant hydrocarboné tel que le benzène, à une température comprise entre 0°C et le point d'ébullition du solvant, facultativement en présence d'une base telle que la pyridine, ou (b) en faisant réagir l'acide quinoléine-carboxylique convenablement substitué avec un thiolate $R^{12}S$ approprié tel que MeSK dan sun solvant tel que le diméthylformamide à une température comprise entre 50°C et le point de reflux de solvant, ou (c) en dissolvant l'acide quinoléine-carboxylique dans un solvant protique tel que l'éthanol, et en traitant ensuite avec un oxyde ou hydroxyde de métal tel que l'oxyde ou l'hydroxyde de sodium ou de potassium ou une amine telle que le 1-amino-butanol ou la lysine à une température comprise entre 0°C et le point d'ébullition du solvant employé et en préparant facultativement un sel d'un groupe amino en dissolvant l'amine dans un solvant tel que l'éther d'éthyle et en ajoutant un acide minéral tel que HCl; ou (d) en traitant le sel, (c), par traitement avec un réactif tel que $SOCl_2$ ou le chlorure d'oxalyle dans un solvant inerte tel que le benzène à une température comprise entre 25°C et le point d'ébullition du solvant employé pour former un halogénure d'acide, puis en ajoutant un alcool, $R^{11}OH$, dans un solvant tel que le tétrahydrofuranne à une température comprise entre 10°C et le point d'ébullition du solvant employé, facultativement en présence d'une base telle que la pyridine, la triéthylamine ou la 4-diméthylaminopyridine.

30. Un procédé pour préparer les composés de la revendication 28, consistant essentiellement (1) à faire réagir une isatine convenablement substitutée (IV) avec une cétone substitutée (V) dans un solvant tel que l'éthanol avec une base telle que la diéthylamine ou la triéthylamine à une température de 25°C à 50°C pendant 2 à 48 heures, (2) à dissoudre le composé intermédiaire (VI) résultant dans un solvant approprié tel que le tetrahydrofuranne contenant 25 à 50% en volume d'un acide minéral tel que HCl et chauffer entre 50°C et la température de reflux du mélange dissolvant pendant 2 à 48 heures, et, facultativement, à faire réagir encore l'acide quinoléine-carboxylique venant de (2) ci-dessus (a) en acylant le groupe hydroxyle correspondant, lorsque R est OH, avec un halogénure carboxylique tel que le chlorure de benzoyle dans un solvant inerte tel que le chloroforme ou un solvant hydrocarboné tel que le benzène à une température comprise entre 0°C et le point d'ébullition du solvant, facultativement en présence d'une base telle que la pyridine, ou (b) en faisant réagir l'acide quinoléine-carboxylique convenablement substitué avec un thiolate $R^{12}S$ approprié tel que MeSK dans un solvant tel que le diméthylformamide à une température comprise entre 50°C et la température de reflux du solvant, ou (c) en dissolvant l'acide quinoléine-carboxylique dans un solvant protique tel que l'éthanol, puis en traitant avec un oxyde ou hydroxyde de métal tel que l'oxyde ou l'hydroxyde de sodium ou de potassium, ou une amine telle que le 1-amino-butanol ou la lysine, à une température comprise entre 0°C et le point d'ébullition du solvant employé et en préparant facultativement un sel d'un groupe amino en dissolvant l'amine dans un solvant tel que l'éther d'éthyle et en ajoutant un acide minéral tel que HCl; ou (d) en traitant le sel, (c), par traitement avec un réactif tel que $SOCl_2$ ou le chlorure d'oxalyle dans un solvant inerte tel que le benzène à une température comprise entre 25°C et le point d'ébullition du solvant employé pour former un halogénure d'acide, puis en ajoutant un alcool, $R^{11}OH$, dans un solvant tel que le tétrahydrofuranne à une température comprise entre 10°C et le point d'ébullition du solvant employé, facultativement en présence d'une base telle que la pyridine, la triéthylamine ou la 4-diméthylaminopyridine.

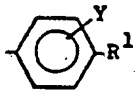
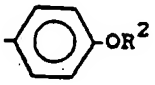
Revendications pour l'Etat contractant: AT

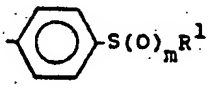
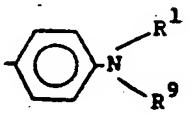
1. Procédé pour préparer une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé répondant à la formule:

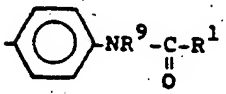
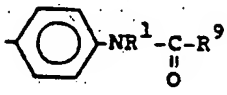


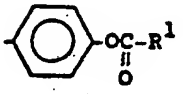
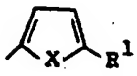
(I)

dans laquelle

R est  .  .

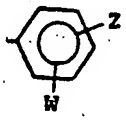
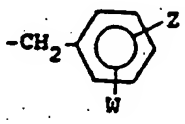
 .  .

 .  .

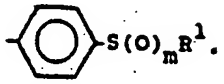
 . ou  ;

X est O, $S(O)_q$, NH ou CH=N;

R^1 est un groupe $CH_3CH_2(CH_3)CH$, alkyle de 5 à 12 atomes de carbone, alcényle de 5 à 12 atomes de carbone, cycloalkyle de 3 à 7 atomes de carbone, cycloalkylalkyle de 5 à 12 atomes de carbone, cycloalcényle de 5 à 7 atomes de carbone,

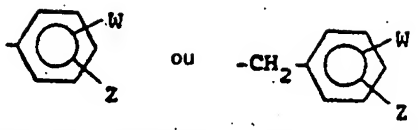
 ou  .

lorsque

R est  .

R^1 peut être, de plus, un groupe alkyle de 3 ou 4 atomes de carbone;

R^2 est



;

R^3 est H, un groupe alcoxy de 1 à 3 atomes de carbone, alkylthio de 1 à 3 atomes de carbone ou alkyle de 1 à 3 atomes de carbone facultativement substitué par un ou plusieurs de F, Cl, Br ou $(CH_2)_pCOR^{10}$ où p est 1, 2, 3 ou 4;

R^4 est CO_2H ou CO_2R^{11};

R^5, R^6, R^7 et R^8 sont indépendamment H, F, Cl, Br, I, CH_3, CF_3, $S(O)_nR^{12}$ ou CH_2CH_3, au moins deux de R^5, R^6, R^7 et R^8 étant H;

R^9 et R^{9A} sont indépendamment H ou un groupe alkyle de 1 à 3 atomes de carbone;

R^{10} est OH, OCH_3, OCH_2CH_3, NH_2, $NHCH_3$ ou $N(CH_3)_2$;

R^{11} est $(CH_2)_{2-4}NR^9R^{9A}$;

R^{12} est un groupe alkyle de 1 à 5 atomes de carbone facultativement substitué par un ou plusieurs de F, Cl et Br;

W, Y et Z sont indépendamment H, F, Cl, Br, un groupe alkyle de 1 à 5 atomes de carbone, NO_2, alcoxy de 1 à 5 atomes de carbone, alkylthio de 1 à 5 atomes de carbone, OH, CF_3 ou NH_2;

m est 0 ou 1;

n est 0 ou 1; et

q est 0, 1 ou 2;

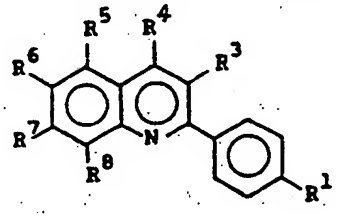
ou un sel pharmaceutiquement acceptable de ce composé; avec les conditions suivantes:

1) R^5, R^6 et R^7 ne peuvent pas tous être H;

2) si R^4 est $CO_2CH_2CH_2N(CH_3)_2$, R^6 est CH_2CH_3 ou R^7 est Cl, R^1 ne peut pas être un groupe cyclohexyle; et

3) si R^1 est un groupe cyclohexyle et R^3 est H, R^6 doit être Cl ou F, mais R^6 et R^8 ne peuvent pas être tous deux Cl, qui consiste à mélanger au moins un composé avec un support pharmaceutique approprié.

2. Procédé pour préparer une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé répondant à la formule:



(II)

dans laquelle

R^1 est un groupe cycloalkyle de 3 à 7 atomes de carbone; phényle; phényle substitué par un halogène, un groupe alkyle de 1 à 5 atomes de carbone ou CF_3; phénoxy; ou phénoxy substitué par un halogène ou un groupe alkyle de 1 à 5 atomes de carbone;

R^3 est H ou un groupe alkyle de 1 à 3 atomes de carbone;

R^4 est CO_2H ou son sel de sodium ou de potassium;

R^5 et R^6 sont indépendamment H, un halogène, CH_3 ou CF_3; et

R^7 et R^8 sont indépendamment H ou un halogène

ou un sel pharmaceutiquement acceptable de ce composé; avec la condition que R^5, R^6 et R^7 ne peuvent pas tous être H et que si R^1 est un groupe cyclohexyle et R^3 est H, R^6 doit être Cl ou F, mais R^6 et R^8 peuvent pas être tous deux Cl, qui consiste à mélanger au moins un composé et un support ou véhicule pharmaceutique approprié.

3. Procédé pour préparer une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 21, qui consiste à mélanger au moins un composé et un support ou véhicule pharmaceutique approprié.

4. Procédé pour préparer une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 22, qui consiste à mélanger au moins un composé et un support ou véhicule pharmaceutique approprié.

5. Procédé pour préparer une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 23, qui consiste à mélanger au moins un composé et un support ou véhicule pharmaceutique approprié.

6. Procédé pour préparer une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 24, qui consiste à mélanger au moins un composé et un support ou véhicule pharmaceutique approprié.

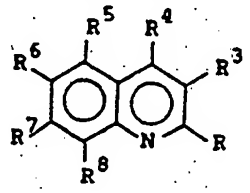
7. Procédé pour préparer une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 25, qui consiste à mélanger au moins un composé et un support ou véhicule pharmaceutique approprié.

8. Procédé pour préparer une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 26, qui consiste à mélanger au moins un composé et un support ou véhicule pharmaceutique approprié.

9. Procédé pour préparer une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 27, qui consiste à mélanger au moins un composé et un support ou véhicule pharmaceutique approprié.

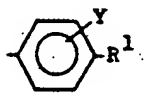
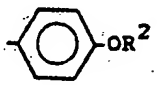
10. Procédé pour préparer une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 28, qui consiste à mélanger au moins un composé et un support ou véhicule pharmaceutique approprié.

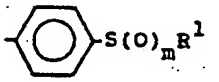
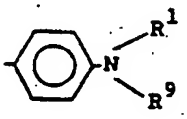
11. Utilisation d'au moins un composé répondant à la formule:

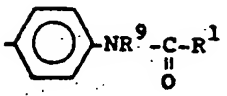
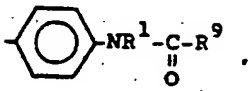


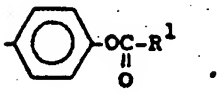
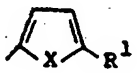
(I)

dans laquelle

R est  .  .

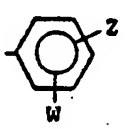
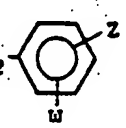
 .  .

 .  .

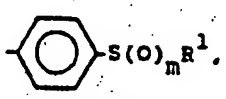
 . ou  :

X est O, $S(O)_q$, NH ou CH=N;

R^1 est un groupe $CH_3CH_2(CH_3)CH$, alkyle de 5 à 12 atomes de carbone, alcényle de 5 à 12 atomes de carbone, cycloalkyle de 3 à 7 atomes de carbone, cycloalkylalkyle de 5 à 12 atomes de carbone, cycloalcényle de 5 à 7 atomes de carbone,

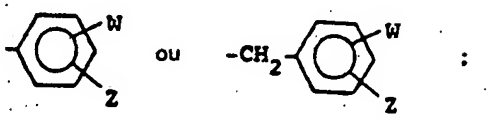
 ou  .

lorsque

R est  .

R^1 peut être, de plus, un groupe alkyle de 3 ou 4 atomes de carbone;

R^2 est



ou

:

R^3 est H, une groupe alcoxy de 1 à 3 atomes de carbone, alkylthio de 1 à 3 atomes de carbone ou alkyle de 1 à 3 atomes de carbone facultativement substitué par un ou plusieurs de F, Cl, Br ou $(CH_2)_pCOR^{10}$ où p est 1, 2, 3 ou 4;

R^4 est CO_2H ou CO_2R^{11};

R^5, R^6, R^7 et R^8 sont indépendamment H, F, Cl, Br, I, CH_3, CF_3, $S(O)_nR^{12}$ ou CH_2CH_3, au moins deux de R^5, R^6, R^7 et R^8 étant H;

R^9 et R^{9A} sont indépendamment H ou un groupe alkyle de 1 à 3 atomes de carbone;

R^{10} est OH, OCH_3, OCH_2CH_3, NH_2, $NHCH_3$ ou $N(CH_3)_2$;

R^{11} est $(CH_2)_{2-4}NR^9R^{9A}$;

R^{12} est un groupe alkyle de 1 à 5 atomes de carbone facultativement substitué par un ou plusieurs de F, Cl et Br;

W, Y et Z sont indépendamment H, F, Cl, Br, un groupe alkyle de 1 à 5 atomes de carbone, NO_2, alcoxy de 1 à 5 atomes de carbone, alkylthio de 1 à 5 atomes de carbone, OH, CF_3 ou NH_2;

m est 0 ou 1;

n est 0 ou 1; et

q est 0, 1 ou 2;

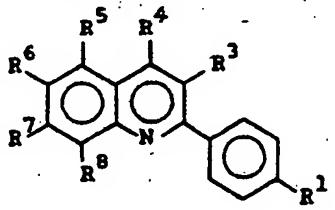
ou un sel pharmaceutiquement acceptable de ce composé; avec les conditions suivantes:

1) R^5, R^6 et R^7 ne peuvent pas tous être H;

2) si R^4 est $CO_2CH_2CH_2N(CH_3)_2$, R^6 est CH_2CH_3 ou R^7 est Cl, R^1 ne peut pas être un groupe cyclohexyle; et

3) si R^1 est un groupe cyclohexyle et R^3 est H, R^6 doit être Cl ou F, mais R^6 et R^8 ne peuvent pas être tous deux Cl, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

12. Utilisation d'au moins un composé répondant à la formule:



(II)

dans laquelle

R^1 est un groupe cycloalkyle de 3 à 7 atomes de carbone; phényle; phényle substitué par un halogène, un groupe alkyle de 1 à 5 atomes de carbone ou CF_3; phénoxy; ou phénoxy substitué par un halogène ou un groupe alkyle 1 à 5 atomes de carbone;

R^3 est H ou un groupe alkyle de 1 à 3 atomes de carbone;

R^4 est CO_2H ou son sel de sodium ou de potassium;

R^5 et R^6 sont indépendamment H, un halogène, CH_3 ou CF_3; et

R^7 et R^8 sont indépendamment H ou un halogène

ou un sel pharmaceutiquement acceptable de ce composé; avec la condition que R^5, R^6 et R^7 ne peuvent pas tous être H et que si R^1 est un groupe cyclohexyle et R^3 est H, R^6 doit être Cl ou F, mais R^6 et R^8 peuvent pas être tous deux Cl, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

13. Utilisation d'au moins un composé de la revendication 21, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

14. Utilisation d'au moins un composé de la revendication 22, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

15. Utilisation d'au moins un composé de la revendication 23, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

16. Utilisation d'au moins un composé de la revendication 24, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

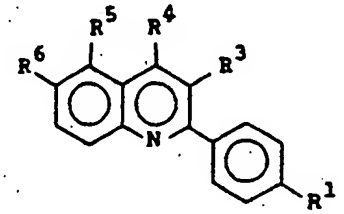
17. Utilisation d'au moins un composé de la revendication 25, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

18. Utilisation d'au moins un composé de la revendication 26, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

19. Utilisation d'au moins un composé de la revendication 27, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

20. Utilisation d'au moins un composé de la revendication 28, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

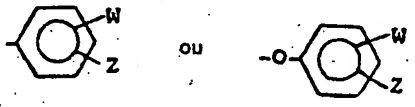
21. Un procédé pour préparer un composé répondant à la formule:



(III)

dans laquelle

R^1 est un groupe cycloalkyle de 3 à 7 atomes de carbone,



;

R^3 est H ou un groupe alkyle de 1 à 3 atomes de carbone;

R^4 est CO_2H ou son sel de sodium ou de potassium;

R^5 et R^6 sont indépendamment H, un halogène ou CF_3, avec la condition que R^5 et R^6 ne soient pas tous deux de l'hydrogène; et

W et Z sont indépendamment H, un halogène, un groupe alkyle de 1 à 5 atomes de carbone ou CF_3; avec la condition que si R^1 est un groupe phényle ou phénoxy et R^5 est H, alors R^6 ne peut pas être Br; et que si R^1 est un groupe cyclohexyle et R^3 est H, R^6 doit être Cl ou F, qui consiste (1) à faire réagir une isatine convenablement substituée (IV) avec une cétone substituée (V) dans un solvant tel que l'éthanol avec une base telle que la diéthylamine ou la triéthylamine à une température de 25°C à 50°C pendant 2 à 48 heures, (2) à dissoudre le composé intermédiaire (VI) résultant dans un solvant approprié tel que le tetrahydrofuranne contenant 25 à 50% en volume d'un acide minéral tel que HCl et chauffer entre 50°C et la température de reflux du mélange dissolvant pendant 2 à 48 heures, et, facultativement, à faire réagir encore l'acide quinoléine-carboxylique venant de (2) ci-dessus (a) en acylant le groupe hydroxyle correspondant, lorsque R est OH, avec un halogénure carboxylique tel que le chlorure de benzoyle dans un solvant inerte tel que le chloroforme ou un solvant hydrocarboné tel que le benzène à une température comprise entre 0°C et le point d'ébullition du solvant, facultativement en présence d'une base telle que la pyridine, ou (b) en faisant réagir l'acide quinoléine-carboxylique convenablement substitué avec un thiolate $R^{12}S$ approprié tel que MeSK dans un solvant tel que le diméthylformamide à une température comprise entre 50°C et la température de reflux du solvant, ou (c) en dissolvant l'acide quinoléine-carboxylique dans un solvant protique tel que l'éthanol, puis en traitant avec un oxyde ou hydroxyde de métal tel que l'oxyde ou l'hydroxyde de sodium ou de potassium, ou une amine telle que le 1-amino-butanol ou la lysine, à une température comprise entre 0°C et le point d'ébullition du solvant employé et en préparant facultativement un sel d'un groupe amino en dissolvant l'amine dans un solvant tel que l'éther d'éthyle et en ajoutant un acide minéral tel que HCl; ou (d) en traitant le sel, (c), par traitement avec un réactif tel que $SOCl_2$ ou le chlorure d'oxalyle dans un solvant inerte tel que le benzène à une température comprise entre 25°C et le point d'ébullition du solvant employé pour former un halogénure d'acide, puis en ajoutant un alcool, $R^{11}OH$, dans un solvant tel que le tétrahydrofuranne à une température comprise entre 10°C et le point d'ébullition du solvant employé, facultativement en présence d'une base telle que la pyridine, la triéthylamine ou la 4-diméthylaminopyridine.

22. Un procédé de la revendication 21, dans lequel:

R^1 est un groupe phényle, phényle substitués par au moins un halogène ou groupe phénoxy, ou phénoxy substitué par au moins un halogène;

R^3 est un groupe méthyle;

R^5 est H ou Cl; et

R^6 est F ou Cl.

23. Le procédé de la revendication 21, dans lequel le composé préparé est le sel de sodium ou de potassium de l'acide 2 - (1,1' - diphényl - 4 - yl) - 6 - fluoro - 3 - méthyl - 4 - quinoléine-carboxylique.

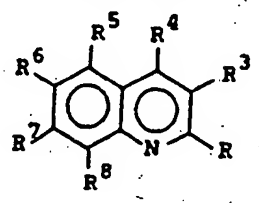
24. Le procédé de la revendication 21, dans lequel le composé préparé est le sel de sodium ou de potassium de l'acide 6 - fluoro - 3 - méthyl - 2 - (4 - phénoxyphényl) - 4 - quinoléine-carboxylique.

25. Le procédé de la revendication 21, dans lequel le composé préparé est le sel de sodium ou de potassium de l'acide 2 - (4' - bromo - 1,1' - diphényl - 4 - yl) - 6 - fluoro - 3 - méthyl - 4 - quinoléine-carboxylique.

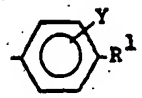
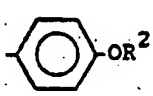
26. Le procédé de la revendication 21, dans lequel le composé préparé est le sel de sodium ou de potassium de l'acide 2 - (2' - fluoro - 1,1' - diphényl - 4 - yl) - 6 - fluoro - 3 - méthyl - 4 - quinoléine-carboxylique.

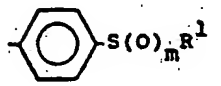
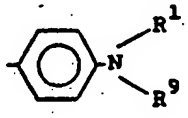
27. Le procédé de la revendication 21, dans lequel le composé préparé est le sel de sodium ou de potassium de l'acide 2 - (1,1' - diphényl - 4 - yl) - 5 - chloro - 6 - fluoro - 3 - méthyl - 4 - quinoléine-carboxylique.

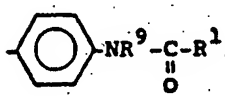
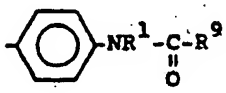
28. Procédé pour préparer un composé répondant à la formule:

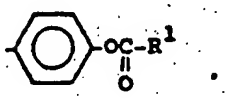
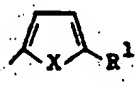


dans laquelle

R est  .  .

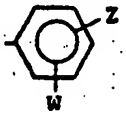
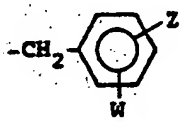
 .  .

 .  .

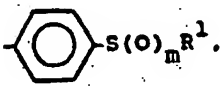
 . ou  ;

X est O, $S(O)_q$, NH ou CH=N;

R^1 est un groupe $CH_3CH_2(CH_3)CH$, alkyle de 5 à 12 atomes de carbone, alcényle de 5 à 12 atomes de carbone, cycloalkyle de 3 à 7 atomes de carbone, cycloalkylalkyle de 5 à 12 atomes de carbone, cycloalcényle de 5 à 7 atomes de carbone,

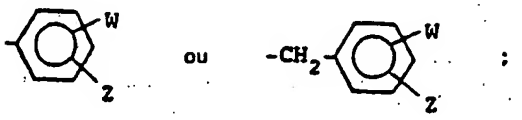
 ou  .

lorsque

R est  .

R^1 peut être, de plus, un groupe alkyle de 3 ou 4 atomes de carbone;

R^2 est



;

R^3 est H, un groupe alcoxy de 1 à 3 atomes de carbone, alkylthio de 1 à 3 atomes de carbone ou alkyle de 1 à 3 atomes de carbone facultativement substitué par un ou plusieurs de F, Cl, Br ou $(CH_2)_pCOR^{10}$ où p est 1, 2, 3 ou 4;

R^4 est CO_2H ou CO_2R^{11};

R^5, R^6, R^7 et R^8 sont indépendamment H, F, Cl, Br, I, CH_3, CF_3, $S(O)_nR^{12}$ ou CH_2CH_3, au moins deux de R^6, R^6, R^7 et R^8 étant H;

R^9 et R^{9A} sont indépendamment H ou un groupe alkyle de 1 à 3 atomes de carbone;

R^{10} est OH, OCH_3, OCH_2CH_3, NH_2, $NHCH_3$ ou $N(CH_3)_2$;

R^{11} est $(CH_2)_{2-4}NR^9R^{9A}$;

R^{12} est un groupe alkyle de 1 à 5 atomes de carbone facultativement substitué par un ou plusieurs de F, Cl et Br;

W, Y et Z sont indépendamment H, F, Cl, Br, un groupe alkyle de 1 à 5 atomes de carbone, NO_2, alcoxy de 1 à 5 atomes de carbone, alkylthio de 1 à 5 atomes de carbone, OH, CF_3 ou NH_2;

m est 0 ou 1;

n est 0 ou 1; et

q est 0, 1 ou 2;

ou un sel pharmaceutiquement acceptable de ce composé; avec les conditions suivantes:

1) si R^4 est CO_2H, R^1 est un groupe phényle ou phénoxy et R^6, R^7 et R^8 sont H, R^6 ne peut pas être Br;

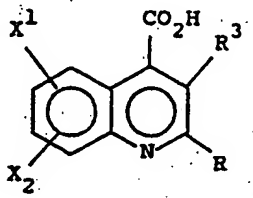
2) R^5, R^6 et R^7 ne peuvent pas tous être H;

3) si R^4 est $CO_2CH_2CH_2N(CH_3)_2$, R^8 est CH_2CH_3 ou R^7 est Cl, R^1 ne peut pas être un groupe cyclohexyle;

4) si R^1 est un groupe cyclohexyle et R^3 est H, R^6 doit être Cl ou F, mais R^6 et R^8 ne peuvent pas être tous deux Cl;

5) si R^1 est 4-$H_2NC_6H_4$ et R^3 est H, R^6 ne peut pas être Cl et R^8 ne peut pas être Br;

6) si R^1 est un groupe alkyle de 6 atomes de carbone et Y est H, alors R^4 ne peut pas être CO_2H, R^5, R^7 et R^8 ne peuvent pas être H, et R^6 neu peut pas être H, Cl, Br, I ou CH_3, caractérisé en ce qu'on fait réagir un acide quinoléine-carboxylique de la formule:



(a) lorsque R est OH, en acylant le groupe hydroxyle avec un halogénure carboxylique tel que le chlorure de benzoyle dans un solvant inerte tel que le chloroforme ou un solvant hydrocarboné tel que le benzène, à une température comprise entre 0°C et le point d'ébullition du solvant, facultativement en présence d'une base telle que la pyridine, ou (b) en faisant réagir l'acide quinoléine-carboxylique substitué avec un thiolate $R^{12}S$ approprié tel que MeSK dans un solvant tel que le diméthylformamide à une température comprise entre 50°C et le point de reflux de solvant, ou (c) en dissolvant l'acide quinoléine-carboxylique dans un solvant protique tel que l'éthanol, et en traitant ensuite avec un oxyde ou hydroxyde de métal tel que l'oxyde ou l'hydroxyde de sodium ou de potassium ou une amine telle que le 1-amino-butanol ou la lysine à une température comprise entre 0°C et le point d'ébullition du solvant employé et en préparant facultativement un sel d'un groupe amino en dissolvant l'amine dans un solvant tel que l'éther d'éthyle et en ajoutant un acide minéral tel que HCl; ou (d) en traitant le sel, (c), par traitement avec un réactif tel que $SOCl_2$ ou le chlorure d'oxalyle dans un solvant inerte tel que le benzène à une température comprise entre 25°C et le point d'ébullition du solvant employé pour former un halogénure d'acide, puis en ajoutant un alcool, $R^{11}OH$, dans un solvant tel que le tétrahydrofuranne à une température comprise entre 10°C et le point d'ébullition du solvant employé, facultativement en présence d'une base telle que la pyridine, la triéthylamine ou la 4-diméthylaminopyridine.

29. Un procédé pour préparer les composés de la revendication 28, consistant essentiellement (1) à faire réagir une isatine convenablement substituée (IV) avec une cétone substituée (V) dans un solvant tel

que l'éthanol avec une base telle que la diéthylamine ou la triéthylamine à une température de 25°C à 50°C pendant 2 à 48 heures, (2) à dissoudre le composé intermédiaire (VI) résultant dans un solvant approprié tel que le tetrahydrofuranne contenant 25 à 50% en volume d'un acide minéral tel que HCl et chauffer entre 50°C et la température de reflux du mélange dissolvant pendant 2 à 48 heures, et, facultativement, à faire réagir encore l'acide quinoléine-carboxylique venant de (2) ci-dessus (a) en acylant le groupe hydroxyle correspondant, lorsque R est OH, avec un halogénure carboxylique tel que le chlorure de benzoyle dans un solvant inerte tel que le chloroforme ou un solvant hydrocarboné tel que le benzène à une température comprise entre 0°C et le point d'ébullition du solvant, facultativement en présence d'une base telle que la pyridine, ou (b) en faisant réagir l'acide quinoléine-carboxylique convenablement substitué avec un thiolate $R^{12}S$ approprié tel que MeSK dans un solvant tel que le diméthylformamide à une température comprise entre 50°C et la température de reflux du solvant, ou (c) en dissolvant l'acide quinoléine-carboxylique dans un solvant protique tel que l'éthanol, puis en traitant avec un oxyde ou hydroxyde de métal tel que l'oxyde ou l'hydroxyde de sodium ou de potassium, ou un amine telle que le 1-aminobutanol ou la lysine, à une température comprise entre 0°C et le point d'ébullition du solvant employé et en préparant facultativement un sel d'un groupe amino en dissolvant l'amine dans un solvant tel que l'éther d'éthyle et en ajoutant un acide minéral tel que HCl; ou (d) en traitant le sel, (c), par traitement avec un réactif tel que $SOCl_2$ ou le chlorure d'oxalyle dans un solvant inerte tel que le benzène à une température comprise entre 25°C et le point d'ébullition du solvant employé pour former un halogénure d'acide, puis en ajoutant un alcool, $R^{11}OH$, dans un solvant tel que le tétrahydrofuranne à une température comprise entre 10°C et le point d'ébullition du solvant employé, facultativement en présence d'une base telle que la pyridine, la triéthylamine ou la 4-diméthylaminopyridine.